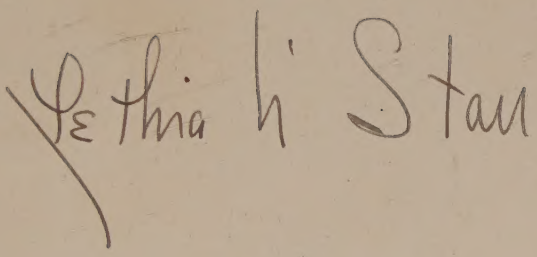

ŒDEMA AND NEPHRITIS

A CRITICAL, EXPERIMENTAL AND CLINICAL STUDY OF THE PHYSIOLOGY AND PATHOLOGY OF WATER ABSORPTION IN THE LIVING ORGANISM

BY

MARTIN H. FISCHER

Doctor of Medicine

Eichberg Professor of Physiology in the University of Cincinnati

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MARTIN H. FISCHER

TO

C. R. F.

Science commences when for a great number of experiences one general conception is found which will embrace all cases. Thus, if you know that a certain remedy has cured Callias of a certain disease and the same remedy has produced the same effect on Socrates and on several other persons, that is Experience, but to know that a certain remedy will cure all persons attacked with the same disease is Science. Experience is the knowledge of individual things. Science is that of Universals.—ARISTOTLE.

PREFACE TO THE THIRD EDITION

I do not deny that the call for a third edition gives me a sense of satisfaction. It means that the ideas here expressed have made their way among the open minded of my profession and this in spite of the fact that what is written in the succeeding pages has been almost universally condemned, even though rarely read through, by those clothed in the robes of authority.

I have found it well in this edition, as in the second, to leave what was written in the first unaltered, except for typographical errors. The changes again consist in additions to the text, which in this volume comprise a more detailed development of the concept of the hydrophilic colloid, the insertion of observations on the swelling of aleuronat, the introduction of further experiments on the swelling and solution of gelatin in non-acid media, a discussion of the nature of the increase and decrease in hydration capacity of the proteins, a broader discussion of the essential nature of water secretion, experimental evidence for the importance of distinguishing between swelling and "solution" in colloids, new pages on the behavior of protein colloids in the presence of buffer mixtures, renewed emphasis on the non-relationship between disease of the kidney and the so-called signs, symptoms and complications of nephritis, additional suggestions regarding the treatment of nephritis and a bolder insistence upon the purely infectious origin of vascular disease with its consequences, including the chronic interstitial nephritis of BRIGHT. I have also taken the liberty of adding in an appendix two articles, somewhat revised, dealing in the first instance with the monumental work of FRANK BILLINGS and his focal infections (of interest because this chapter reiterates the principles and practice to be followed in dealing clinically with infections in and about the teeth) and in the second with a clinical lecture on the classification and treatment of the nephritides. While the substance of each of these papers

appeared even in the second edition, my friends have found the form of these papers particularly helpful, and since they are not readily available in their original places of publication they are reprinted here.

The fact that the original text has not been changed but only added to, may prove of service to those workers in medicine who have any regard for the historical aspects of medical and biological science. It is an ironic fact that I can cite to-day as best proof for the correctness of the general notions for which I have pleaded for more than a decade the observations of the very workers who have been most violent in their criticism of what I have written. The colloid-chemical notions of water absorption by protoplasm with their many physiological and pathological corollaries, so long a jest, are now embodied by these workers in their scientific discussions as self-evident truths in which the original sponsor needs never to be mentioned. High commissions find alkali, glucose and colloid injection mixtures the chief things of service in shock; surgeons suddenly discover that their bad operative risks are "acidosed" and that food and alkali may save them; while those who thought the acid content of the living mass an unchangeable value are running about their wards with respiration bags and hydrogen ion determinators.

The fact that the cellular changes discussed in these pages and characteristic of disease are in essence changes in the colloid state of protoplasm has constituted an ever-present temptation to discuss in greater detail the developments of pure colloid chemistry itself and its interesting theoretical deductions. I have, however, steered clear of all hypothesis so that this edition might remain, as the former ones, intensely practical. The nature of fatty degeneration I have taken up in a volume which has preceded this one.[1] The nature of the action of acids, alkalies and salts upon protoplasm (together with a discussion of the intrinsic character of the changes thus brought about) is corollary to my observations on soaps, a volume covering which subject[2] I hope to have out of hand shortly.

I cannot let this new edition go to print without acknowledging my gratitude to various friends. I owe much to my secretary

[1] "Fats and Fatty Degeneration," John Wiley and Sons, Inc., New York (1917).

[2] "Soaps and Proteins," John Wiley and Sons, Inc., New York. (In press.)

Doris Wulff. Renewed thanks are due Harry M. Levy, who has continued his generous support of the Joseph Eichberg Laboratory in spite of its seeming vagaries. For inspiration to scientific work and for example in perseverance and courage I have times without number turned to the builder of resurgent medical Cincinnati, Christian R. Holmes.

Martin H. Fischer.

University of Cincinnati,
June, 1920.

PREFACE TO THE SECOND EDITION

These pages give in combined form the contents of the 1909 Nathan Lewis Hatfield Prize Essay of the College of Physicians of Philadelphia, and of the 1911 Cartwright Prize Essay of the Alumni of the College of Physicians and Surgeons of Columbia University, New York, previously published as separate volumes bearing the titles "Œdema" and "Nephritis." The close association between the two made their appearance in combined form seem advisable. The chief changes which time has rendered necessary consist of additions to the general text embodying the results of later experimental and clinical observations in good part not readily accessible to English readers—the main argument remains as before.

Throughout the text are mentioned those who with me did the day's work. These references to James J. Hogan, Edmund M. Baehr, Gertrude Moore, Marian O. Hooker, Thomas H. Kelly, Hayward G. Thomas, William H. Strietmann, Anne Sykes and Carl Hiller but ill express my indebtedness to them. Nor would I fail to acknowledge the intelligent and faithful help of my technical assistant, Josef Kupka. In these paragraphs I can only record my keen appreciation of what they did.

To Lauder W. Jones I have often turned for help in matters chemical, to Louis Trenchard More in matters physical. Alfred Brodbeck made possible the observations on athletes. Charles Goosman gave of his time and skill to prepare the photomicrographs. Charles Hecker and Peter Scherrer made many of the other photographs. To all these I would express my sincere thanks.

The now old views restated and elaborated in this volume have not gone unchallenged. Where these challenges have

sprung from scientific doubt it has not been difficult to reach common ground by discussion. Where the personal has entered into the spirit of the attack I have succeeded, in part at least, in keeping silent. As this is my wish for the future, will the interested reader of disputed points examine the evidence away from the noise of the pleading attorneys?

Much of the older work and most of the newer in this volume was shaped in the Joseph Eichberg Laboratory of Physiology in the University of Cincinnati. The atmosphere prevailing there, which recognizes that the new is born as a minority point of view and hence is unpopular, and that the function of a university is to give it sanctuary, has been made possible by the generosity of Harry M. Levy.

Martin H. Fischer.

University of Cincinnati, 1914.

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PART ONE

THE ARGUMENT

ŒDEMA AND NEPHRITIS

PART ONE

THE ARGUMENT

In this first part is given in running form a résumé of the entire volume. The busy reader may accept as much of the argument as here outlined upon the abbreviated evidence accompanying it as he chooses. By turning to the page references given in the text the detailed observations will be found on which are based the more dogmatically stated conclusions contained in these first paragraphs.

PART TWO

So practical a question as the treatment of glaucoma, uremia or anuria is intimately associated with the problem of œdema. This problem of œdema, the question of how a cell, an organism or the body as a whole comes to hold an abnormally large amount of water is in its turn but a subheading of that still greater problem, why living matter holds any water at all and why under normal circumstances it holds so constant an amount. Various hypotheses have been proposed by animal and plant physiologists, by pathologists and clinicians to explain such normal and abnormal water absorption, but all are inadequate to account for more than the smallest fraction of the phenomena observed.

The absorption of water by living matter under physiological and pathological circumstances is determined by the colloids contained in it and their state. The major portion of the chemical substances which make up protoplasm exists there in

colloid form. A discussion of the properties of colloids with particular reference to the matter of water absorption is therefore in order. (See pages 41–44.)

About the middle of the last century it was noted that chemical substances differ in the rate at which they diffuse through solvents. The group which diffuse but slowly and which are for the most part amorphous, of high molecular weight, without osmotic pressure, and pseudo-soluble, are known as colloids, while those which diffuse rapidly, are of low molecular weight, have osmotic pressure, and form true solutions, are known as crystalloids. Among the former are found glue, gelatin, albumin and starch; among the latter, cane sugar, common salt and urea. While we are seemingly classifying substances we should really speak of the colloid and crystalloid states, for later observations have shown that it is not its chemical character which identifies the colloid, but rather the physical state of the substance, practically all substances being capable of existing in either of these two forms. (See pages 44–49.)

The colloids themselves do not all show the same properties. On the one hand there are those which enter into close association with their solvent (lyophilic or hydrophilic colloids); on the other, those which do not (lyophobic or hydrophobic colloids). Gelatin, dextrin, starch, glue, vegetable fibers, albumin and gums are examples of the former class; the colloid metals, metallic hydroxids and sulphids are examples of the latter. (See pages 49–61.)

The former of these two groups is of greatest biological importance, for the bulk of protoplasm is made of it. An attempt is therefore made to define the difference between the two groups more closely. Beginning with the now generally accepted belief that a colloid system results whenever one material is divided into a second with the degree of subdivision coarser than molecular and not yet so coarse as to come into the physical realm of the mechanical mixtures, it is pointed out that a hydrophobic or lyophobic colloid results whenever the subdivided material is not a solvent for the dispersion medium; a hydrophilic or lyophilic colloid when the subdivided material is such a solvent. Illustrations are introduced of the different types of systems that may be thus produced. Beginning at the top is a system consisting of a true solution of *a* in *b* while at the bottom is another true solution of *b* in *a*. Be-

tween these extremes exist two zones of mixed systems, one under the topmost consisting of a subdivision of solvated *a* particles in a solution of *a* in *b*, and below this a system of reverse type, namely, one of a subdivision of a solution of *a* in *b* in hydrated *a* as an enveloping or external phase. On the basis of the existence of these different systems are explained the meanings of such terms as solubility, solvation capacity, swelling, sol and gel, gelation capacity, syneresis and hysteresis.

To discover some of the properties of the lyophilic colloids, particularly their relation to the absorption of solvent, the biologically important colloids, fibrin, gelatin, gluten, aleuronat and blood serum are studied. (See pages 61–151.)

Fibrin absorbs more water (swells more) in any acid solution than it does in pure water. Within certain limits the amount of water thus absorbed increases with the concentration of the acid, but when a certain concentration is exceeded the fibrin swells less than in lower concentrations. The same is true of alkalies. The addition of any salt, even a neutral salt, to the solution of any acid or alkali reduces the amount that the fibrin swells and this the more the higher the concentration of the salt. When equivalent concentrations of different salts are compared some are found more active in this regard than others. Thus, the chlorid, bromid and iodid are less capable of dehydrating fibrin than the acetate, while yet more powerful are the sulphate, phosphate and citrate. When the effects of basic radicals are compared potassium, sodium and ammonium are found less active than magnesium, calcium or strontium, while copper and iron are most effective of all. Non-electrolytes are comparatively ineffective in reducing the swelling in the presence of an acid or alkali. They are not, however, entirely without effect. Among the non-electrolytes the sugars deserve special mention because these produce a considerable dehydrating effect. When dextrose, levulose and saccharose are compared the last named is found particularly powerful. The taking up and giving off of water by fibrin represents in large measure a reversible process. In addition to the acids and alkalies there exist a number of other substances which are capable of increasing its hydration capacity. Urea and pyridin and possibly some of the amins are to be mentioned in this class. The hydrations produced by these substances are of a different type from those

produced by acids and alkalies, for they are not readily reducible through salts, while they are through various non-electrolytes (sugars), a behavior the opposite of that observed in acid or alkali hydration. (See pages 61–75.)

What has been said of fibrin is not characteristic of it alone, but is true of all proteins, as illustrated by the identical behavior of gelatin, gluten and aleuronat. (See pages 75–145.)

What has been said of the solid colloids holds also for the liquid colloids such as blood serum, fluid gelatin or egg white. The hydration and dehydration in such liquid colloids can be followed by noting the changes in their viscosity, hydration being betrayed by an increase in viscosity, dehydration by a decrease. (See pages 145–151.)

The behavior of the more solid colloids corresponds to the behavior of the more solid constituents of our body, as the tissues; that of the liquid with the fluids permeating these solid structures, namely, the blood, the lymph, the cerebro-spinal fluid, etc.

It can be shown that every tissue takes up water or gives it off under conditions identical with those which cause protein colloids to do this. Thus, muscle, eyes or nervous tissues swell more in acid or alkali than in water, and this the more, within certain limits, the higher the concentration. Beyond a certain optimal concentration the tissues begin to lose water. The addition of any salt to the acid or alkali produces a dehydrating effect, and this is the greater the higher the concentration of the salt. At the same concentration different salts are unequally effective, and here again their order parallels that observed on simple proteins. The non-electrolytes as compared with the electrolytes are less effective. The processes of hydration and dehydration in all these tissues are largely reversible. Urea is observed in all these tissues to lead to an increased hydration. (See pages 151–192.)

The acceptance of the view that the colloids of the tissues and their state are primarily responsible for the amount of water held by them constitutes a tacit criticism of every theory of water absorption thus far advanced. These theories may be called for short, the osmotic theory conjointly with which we may consider that modification of it known as the lipoid membrane theory, and the pressure theory. The pressure theory is criticised later. (See pages 193–195.)

The osmotic theory assumes that cells are surrounded by semi-permeable membranes through which water but no dissolved substances can pass. The movement of water is occasioned by differences in the concentration of dissolved substances within and without the cell, the water being carried in the direction of the higher concentration whether existing within or without the cell. In thus accounting for the migration of water into and out of cells it becomes impossible to get dissolved substances through. Such a conception of the living cell is an impossible one because the cell must be and is able to absorb all manner of foodstuffs and get rid of the products of its metabolism. To meet this situation the original osmotic theory has been modified by saying that the membrane is permeable to some or all substances at some or all times. But when this postulate is granted concentration differences between the inside and the outside of the cell can no longer come to pass, for the dissolved substances will simply move from regions of higher to regions of lower concentration. The forces active for the movement of water therefore disappear. Adherents of the osmotic theory can move either water or dissolved substances, but they cannot move both, and yet in living cells this must be possible. (See pages 195–201.)

The lipoid membrane theory suffers from much the same defects as the original osmotic one. In assuming the outer layer of cells to be fatlike in character, it may become possible to explain more easily the entrance of fat-soluble substances, but since fat is no solvent for water, for salts and for many of the normal products of cell metabolism, this conception is also biologically impossible, for all these can and must be able to pass into and out of cells. (See pages 201–203.)

The mosaic theory, which holds part of the cell membrane to be "protoplasmic" in character, another part lipoid, suffers from the combined defects of the osmotic and lipoid theory. (See page 203.)

In the colloid-chemical theory there is no need for membranes about the cells. The absorption of water is governed by the laws which govern the hydration and dehydration of lyophilic colloids. The differences between the concentration of dissolved substances found inside and outside of the cell are accounted for through differences in relative solubility, differences in adsorption and differences in chemical constitution. The cell

conceived of as a colloid matrix can not only absorb and secrete water, but it can also absorb and secrete any dissolved substance at the same time, and the two processes may run in the same direction or in opposite directions as physiological and biological observation demands. (See pages 204–206.)

The conception that cells are surrounded by osmotic or lipoid membranes has been used to explain not only the absorption of water, but also the biological characteristics of the absorption of dissolved substances. In essence this problem asks why different parts of the same cell or different cells bathed by the same blood and lymph do not all hold the same amount of dissolved substance. The membrane theory attempts to explain such concentration differences by saying that the membranes are partially permeable or impermeable to these dissolved substances. In discarding the osmotic conception of water absorption we discarded also this mechanism for the maintenance of concentration differences. What have we to put in its place? (See pages 206–207.)

We are familiar in physical chemistry with a number of illustrations of inequalities in the distribution of dissolved substances between different phases even though no membranes exist between them. Thus, when a substance is more soluble in one solvent than in another, it will collect in greater concentration in that in which it is the more soluble; or the adsorption properties of the colloids may be different as in different cells; or the presence of certain chemical compounds in one phase permits it to combine chemically and so hold a greater amount of a given dissolved substance than another phase in which such are not present or present in less amount. Finally, all three may be active at one and the same time. (See pages 208–213.)

On this basis our conception of the cell becomes that of a mass of protein intimately mixed with more or less fat and fat-like material, the whole immersed in a liquid from which the protein-fat mixture soaks up a certain amount of water and of various substances dissolved in the water, the whole being governed by the laws of equilibrium. (See page 213.)

PART THREE

The problem of œdema is also a problem in colloid-chemistry—that of the ways and means by which the normal hydration capacity of the body colloids is heightened. The school of pathologists quite generally upholds the teaching that œdema is produced by changes in the pressure of the circulating fluids of the body (increased blood and lymph pressure) together with an increase in the permeability of the vessel walls. This pressure theory is completely unsatisfactory, for not only may we have extreme degrees of œdema without changes in blood or lymph pressure, but measures which increase blood pressure and should therefore increase œdema are known to produce just the opposite effect. In place of the pressure idea, changes in the tissues and cells have therefore been made to play a rôle in the development of œdema, but the attempt to define clearly the real nature of these was not made until quite recently when it was taught that increases in the osmotic pressure of the cell contents might lead to an increased absorption of water and thus to œdema. (See pages 217–220.)

The cause of œdema resides in the tissues, which become œdematous not because water is forced into them, but because they suffer changes which make them suck up water. This is proved by the fact that the severest grades of œdema may be produced in the entire absence of any circulation, and consequently in the entire absence of any blood pressure. (See pages 220–232.)

A state of œdema is induced whenever, in the presence of an adequate supply of water, the capacity of the tissue colloids for holding it is increased above that which we are pleased to call normal. Any agency capable, under the conditions existing in the body, of thus increasing the hydration capacity of the tissue colloids constitutes a cause of œdema. The accumulation of acids within the tissues, brought about either through their abnormal production or through the inadequate removal of such as some consider normally produced in the tissues, is chiefly responsible for this increase in the hydration capacity of the colloids, though the possibility of explaining at least some of it through the production or accumulation of substances (of the type of urea, pyridin, certain amins, etc.) which hydrate col-

loids as do acids, or through the conversion of colloids having but little capacity for water into such as have a greater capacity must also be borne in mind. (See pages 232–233.)

As it has already been proved that the amount of water absorbed by a tissue is dependent upon its content of lyophilic colloids it must next be shown that conditions capable of increasing their normal hydration capacity are produced in all states of œdema. Of those that might be discussed, an abnormal production and accumulation of acids is considered the most potent, wherefore it receives detailed consideration. (See page 233.)

The proof that such occurs in all states of œdema consists of the following: An abnormal production or accumulation of acids or conditions predisposing thereto exist in all states in which we encounter œdema. Circulatory disturbances, whether generalized or local, conditions which decrease the oxygen-carrying powers of the blood, as the anemias, various states of inanition, the fevers, the chemical changes following death, as well as poisons of various kinds which are followed by œdema, all represent methods by which the chemistry of the tissues is so altered as to lead to an abnormal production or accumulation of acid in them. (See pages 233–243.)

Conversely, any means by which an abnormal production and accumulation of acid may be brought about in a tissue is followed by an œdema. Thus, the acid production occurring in tissues after death or in poisoning by arsenic, morphin, uranium, chloroform, ether, cocain, etc., is always followed by a retention of water in the body and an œdema. (See pages 243–249.)

Finally, those conditions which are capable of decreasing the hydration of protein colloids decrease œdema, while those which are ineffective in this regard do not do so. Thus, the œdemas developed by amputated frogs' legs laid in water are reduced by all salts, and this the more the higher their concentration. At the same concentration different salts are unequally effective in this regard, and this in the order in which they dehydrate simple proteins swelling in the presence of acid. To meet the criticism that such reduction of œdema is possible in "dead" frogs' legs but not in "living" animals, a parallel series of experiments is introduced on "living" frogs made œdematous by injections of uranium. Sodium chlorid is no exception to the

rule; it reduces œdema as does any other salt. (See pages 249–262.)

The possible rôle of other agencies besides an increased acid content in the development of œdema is discussed, and the importance of such known hydrating substances of protein as the alkalies, urea, pyridin and the amins is emphasized. (See pages 262–268.)

A number of the specific problems presented by œdema as it affects special organs is next considered. Thus, another explanation must be found for the generally accepted belief that the œdema observed in a passively congested kidney, produced, for example, by ligation of the renal vein, is due to an increased capillary pressure and a forcing of fluid into the kidney tissues. Ligation of the renal artery with its consequent decrease in blood pressure is followed by exactly the same kind of change. (See pages 268–271.)

Such a result, which cannot be interpreted by any of the older work, is readily understood on the colloid-chemical basis. Whether we deprive an organ of its oxygen supply by preventing the normal efflux of blood from it, or by preventing the normal influx, the resulting accumulation and production of acid is, of course, the same, and so it was to be anticipated that the organ would swell equally in both cases. (See pages 271–276.)

This idea can be further tested on the liver, which besides having a (venous) blood supply through the portal vein, receives a second (arterial) blood supply through the hepatic artery, the two blood streams leaving the liver through the hepatic vein. Ligation of the portal vein does not lead to an oedema of the liver, but an extreme grade of it is produced when the hepatic artery is tied, even though there results herefrom a fall in blood pressure. Passive congestion œdema of the liver secondary to heart disease is really produced through interference with the normal oxygen supply to the parenchyma of the liver through the hepatic artery due either to a deficient blood flow because of a defectively acting heart, or because the overfilled veins dam back the arterial blood so that it cannot get into the liver. (See pages 272–276.)

The problem of pulmonary œdema is essentially the same as that of the passive congestion œdema of the liver, for the lung also has two blood supplies, the pulmonary circuit and a

supply of arterial blood through the bronchial arteries. While interferences with the pulmonary circuit scarcely lead to an œdema of the lungs, such is promptly produced by interference with the systemic circulation. The most potent method of producing a pulmonary œdema consists in interfering with the oxygen supply through the bronchial arteries. (See pages 276–282.)

It remains to account for the accumulations of fluid, so frequently encountered in states of œdema, in the serous cavities and "tissue spaces." These accumulations represent dilute solutions of protein. The squeezing off of such dilute colloid mixtures (the "transudates") by more concentrated and solid ones (the œdematous tissues) is analogous to the syneresis exhibited by colloids. When heavily hydrated solid colloids such as silicic acid or gelatin are permitted to stand, a thin colloid solution separates from them after a time. Such separation is not noted in slightly hydrated colloids, but is marked in heavily hydrated ones, and increases with time. In the same way the severer and more chronic types of œdema are the most likely to be accompanied by accumulations of fluid in the serous cavities and "spaces." (See pages 283–285.)

Some concluding sentences indicate how the experimental findings on œdema of older observers are to be interpreted in the terms of the colloid-chemical theory. (See pages 285–289.)

PART FOUR

The problem of absorption and secretion in the higher animals seems at first sight very different from this same problem in so simple a structure as the individual cell or tissue. The ameba, for instance, takes up or gives off water according to changes in its surroundings, whereas in a complex organism we find whole organs seemingly set apart for absorption or secretion alone. But we need to appreciate that the mucosal cell, for example, is an absorbing cell only so long as we look at it from the side of the lumen of the gut. From the blood vessel side it is a secreting cell, for what it absorbs from the gut it gives up to the blood. What characterizes absorption and secretion in the higher animals is that under normal circumstances and from the point of view of the organism as a whole, absorption and secretion occur predominantly in one direction. The reason for this resides in the

fact that unlike the ameba which is surrounded on all sides by the same medium, the cells of an absorbing or secreting organ (in a mammal, for example) are through different portions of their cell protoplasm in contact with entirely different media. The effort to get into equilibrium with these produce all the phenomena of absorption and secretion characteristic of the higher animals. (See pages 293–296.)

Every absorbing system consists of three phases:

1. The material to be absorbed—essentially an aqueous solution of dissolved substances.

2. An absorbing membrane—physico-chemically, a solid colloid behaving not unlike a leaf of gelatin.

3. The blood and lymph—a liquid colloid acting, as a whole, like a (liquid) solution of gelatin. With it are admixed various solid colloids known as blood cells. (See pages 296–299.)

In discussing absorption we must at all times distinguish between the absorption of water and the absorption of the dissolved substances in the water. Absorption from the peritoneal cavity is first taken up. When water is introduced into the peritoneal cavity it is quickly absorbed. This is because the colloids of the peritoneum in consequence of their constant carbonic acid production are not saturated with water. When the arterial blood enters the peritoneum the carbonic acid produced in the cells is given off to it. This increases the hydration capacity of the blood colloids, which therefore take water out of the peritoneum. As long as the circulation is maintained and the cells continue to produce carbonic acid, absorption of water must therefore occur. (See pages 299–306.)

All salt solutions are absorbed more slowly than pure water. This is because the salts diffuse into the colloid absorbing membrane and tend to dehydrate it, thus starting a counterstream of water secretion to meet the normal stream of water absorption. The end result so far as the absorption of water is concerned will represent the algebraic sum of the two. The higher the concentration of the salt solution the greater the counterstream and consequently the slower the absorption of water from the peritoneal cavity. (See pages 306–307.)

At the same concentration the different salts in solution delay in different degrees the absorption of water, and this in the order in which they tend to dehydrate protein colloids. The non-

electrolytes as compared with the electrolytes are rather ineffective. Only glycerin and the sugars delay definitely the absorption of water by the peritoneum. Both acids and alkalies delay it also. When water is offered the peritoneum in the form of a colloid solution, in a form, therefore, in which it is bound to the colloid, it cannot be absorbed. This is why blood, lymph and ascitic accumulations remain for long periods in the peritoneum, while pure water, dilute salt solutions, etc., are readily absorbed. (See pages 307–311.)

The available facts on the absorption of water by the intestine are explained in identical fashion. Water is absorbed best, and colloid solutions, in which all the water is bound to the colloid, not at all. All salts delay the absorption of water, and this the more the higher the concentration of the salt. Different salts at the same concentration are unequally effective in this regard. A saline cathartic is merely a salt which is very powerful in its dehydrating effect without possessing marked poisonous action. (See pages 311–315.)

Critical remarks on previous theories of absorption are entered into and the laws governing the absorption of dissolved substances discussed. (See pages 315–325.)

Secretion represents the mirror image of absorption. In this problem, as in absorption, we need again to distinguish between the secretion of water and the secretion of any dissolved substance in the water. As the kidney represents from both a qualitative and a quantitative point of view the great secreting organ of our bodies, it receives chief consideration, though what is said of it may with little modification be applied to any of the other secretory organs, as the skin, salivary glands or stomach. (See pages 325–326.)

A secreting system in a complex organism is made up of three phases:

1. A secretion which for the most part represents a watery solution of various crystalloids.

2. A secreting membrane which may be likened to a solid colloid like a leaf of gelatin.

3. A source of some kind, the liquid colloid known as blood or lymph. (See pages 326–327.)

A model is described which illustrates some phases of urinary secretion. It consists of a layer of fibrin through which solutions

of various kinds may pass at constant pressure. Water or a " physiological " salt solution passes through at a certain rate. An acid solution makes the fibrin swell and lowers the amount of " secretion " to the point of stoppage. When to this acid is added any salt the fibrin shrinks and the secretion recommences, the saline diuretics acting more powerfully in this regard than other salts. When acid passes through, the fibrin goes into solution so that an albumin ring is obtainable; this also disappears on the addition of salts. (See pages 327–330.)

The kidney can secrete water only as it is furnished this organ in " free " form. In absolute starvation no free water comes to the kidney and so secretion ceases. On the other hand, the giving of water by mouth, intraperitoneally, subcutaneously or intravenously, increases the secretion according to the amount given (loss through lungs, skin, etc., ignored). (See pages 330–331.)

When sodium chlorid solutions of different concentrations are injected intravenously, the amount of urine given off increases with the concentration of the salt, a point being finally reached where the water output is greater than the amount injected. Such a result is usually interpreted by saying that the salt "stimulates" the kidney and thus, as it were, pulls water out of the blood. What really happens is that the salt content of all the tissues of the body is increased, in consequence of which they give up water, and this " free " water is then added to the amount that is being injected. The " diuretic " action, therefore, really depends primarily upon an effect on the body as a whole and only incidentally on the kidney. (See pages 331–336.)

The conclusion that only free water can be given off by the kidney can be tested by injecting instead of a salt solution a colloid solution in which all the water is bound to the colloid. Injection of no amount of blood or blood serum increases the output of water from the kidney. (See pages 336–339.)

The saline diuretics produce their diuretic action as do the stronger sodium chlorid solutions by their effect upon the body as a whole. They act primarily not upon the kidney, but after injection intravenously diffuse into the tissues, and, dehydrating them, aid in bringing free water to the kidney. The diuretic action of any salt is predictable by adding together the dehydrating effect of its constituent radicals upon a simple protein. (See pages 339–349.)

Those non-electrolytes which are capable of producing some dehydration of simple protein colloids are also able to dehydrate the body colloids and so to produce diuresis. This diuretic action is again to be attributed, in the main, not to an effect upon the kidney, but to an effect upon the body as a whole. Just as dextrose and levulose produce equal degrees of dehydration in simple protein colloids, they have when injected intravenously an equal diuretic action. Saccharose, on the other hand, which acts more powerfully on pure proteins, also acts more powerfully as a diuretic. As the sugars are relatively more effective in producing protein dehydration in high concentrations than in lower ones (the opposite of what is true for salts), they also produce a relatively greater diuresis in the higher concentrations than in the lower. The dehydrating effect of sugar helps to explain not only the dryness of the diabetic's tissues, but his thirst and his increased urinary output. (See pages 349–357.)

In order to secrete properly the kidney must be well supplied with oxygen. This explains why every scheme which interferes with the normal oxygen supply to the kidney or with the proper utilization of oxygen in the kidney is followed by a diminution in the urinary output. Agencies which are capable of aiding in the restoration of a normal oxygen supply to a kidney suffering from its lack constitute a second method of producing diuresis. This is why caffein and its derivatives, digitalis, etc., which favor respiration and the circulation of arterial blood through the kidney, act as diuretics, while, on the other hand, chloroform, ether and alcohol which in large doses lead, *in toto*, to a state of lack of oxygen in the tissues, all decrease the urinary output. Drugs like caffein, digitalis, etc., I shall call for short diuretics of the second order. (See pages 357–362.)

The soundness of these ideas on urinary secretion is tested by applying them to the interpretation of the experimental results of other authors. (See pages 362–365.)

It is pointed out that the transition from the physiological to the pathological in kidney function is not abrupt, but that we pass gradually from such a state as is considered normal to that in which we recognize the pathological extreme of a parenchymatous nephritis. (See pages 365–367.)

The secretion of dissolved substances by the kidney (or any other organ) is a problem that must be considered independently

of the secretion of water. A secretion of water is necessary before we can get the secretion of any dissolved substance. Urine is secreted primarily as water, and only secondarily as it washes down the tubules do substances come to be dissolved in it, giving it the qualities of urine. The feature which it has been difficult to explain in secretion is the quantitative differences between the concentration of any dissolved substance in the blood and the concentration of this same substance in the urine. Upon the existence of such differences has been based a faith in a "vital" element in secretion. Actually, such a conception is premature if not absurd. The distribution of a dissolved substance between any three such phases as blood, kidney substance and water (the original urine) is a matter of equilibrium, and this is by no means always attained when the concentration is the same in all. The equilibrium point may be shifted in either direction, depending upon the solution properties, the adsorption characteristics and the chemical nature of the three phases. (See pages 367–370.)

A second urinary model is described to show how many of the "mysterious" properties of such a secretory system as that represented by the kidney may be understood in the simple terms of colloid chemistry. The kidney parenchyma is compared with a hydrolyzable salt, like ferric chlorid or sodium-gelatin-phosphate, subject to dialysis against water. The ferric chlorid or protein salt undergo hydrolysis with the one fraction (iron or protein) coming down in colloid form while the other (the acid) being crystalloid and readily diffusible passes into the surrounding water to yield a "secretion" more acid than the medium from which it is derived. This is normal urinary secretion in which circumstances a solution of crystalloids, acid in reaction, is being obtained from a less acid colloid matrix. If acid is introduced into the colloid matrix it makes this "go into solution" wherefore iron or protein appears in the surrounding wash water. This is the analog of the "solution" of the kidney proteins in the urine when the kidney is subjected to the action of an accumulation of acids or like-acting substances. (See pages 371–380.)

The question of the mechanism by which water is secreted from such a secreting parenchyma as the kidney is raised in a third model of secretion. The evidence is reviewed which supports the conclusion that such secretion represents a mere filtration process

and since the secreting parenchyma of such an organ as the kidney is a hydrated colloid with properties closely akin to a solid hydrated soap, the filtration properties of such a soap are studied. Cups of solid sodium stearate are chosen. Water passes through such a cup only when free; hydrated liquid colloids comparable to blood remaining in the cup indefinitely. Salt solutions filter through more rapidly than plain water according to (*a*) their concentration and (*b*) their kind. The higher the concentration the more rapid the filtration. On the other hand, salts of ammonium or potassium produce less filtration than salts of sodium and these less than those of magnesium or calcium (just as in the case of urinary secretion in an animal). When the effects of equally concentrated salts with the same basic but different acid radicals are compared, no such diuretic differences appear as occur in animals. The theory of the action of these effects is discussed, it being pointed out that because of the existent differences in chemical composition of fatty acids and of the polymerized amino-acids known as protein, it is possible in the former to produce only one series of salts (as different bases are introduced into the fatty acids) while in the case of the proteins a similar series may be produced but, because of the existence in the latter of NH_2 groups, a second series may also be produced through the linking of acid with these groups. Colloid-chemical and physiological behavior are then an expression of the solvation and solubility properties of the different compounds thus formed. (See pages 380–397.)

The formation of lymph is in many respects analogous to the secretion of urine and is governed by similar laws. Anything that makes the cells or tissues of an organ give up water increases lymph flow, a lymphagogue being any substance which will aid in dehydrating the tissues of the body. (See pages 397–398.)

Some remarks on the vasomotor mechanism follow. Changes in the amount of blood going to a gland are controlled by this. As we would expect, vasodilatation with its better supply of oxygen and free water makes for secretion, while vasoconstriction does the reverse. Vasodilatation with an adequate arterial blood flow may take place and yet there be no secretion from a gland, but only when poisons have been introduced which keep the gland from utilizing the oxygen. During their so-called periods of rest the gland cells swell and develop granules, while during activity they shrink and the granules disappear. The compli-

cated interpretation given these facts is replaced by the simple statement that in the absence of a circulation the gland cells develop an oedema which disappears when the blood vessels dilate and more oxygen becomes available. The granules represent precipitates of a second colloid as the acid content runs up, which disappear when with a better oxygen supply the acid is removed. A so-called resting gland represents the parallel of what in pathology we call cloudy swelling. The existence of secretory nerves is questioned. They are vasomotor nerves. The distribution of secretory nerves and vasomotor nerves is identical. Secretion does not occur without coincident vasodilatation. Vasodilatation may occur without secretion, as when defectively oxygenated blood is furnished, but the reverse, never. A large arterial blood supply is furnished to some glands constantly, to others temporarily through vasodilatation governed by nerves. (See pages 398–400.)

Whatever favors secretion interferes with absorption, and *vice versa*. (See pages 400–403.)

Looking at the problem of secretion from another viewpoint it is now asked why all the blood does not pass out of the body as urine or some other secretion. Why does the blood remain in the blood vessels? The blood remains in them because all its water is bound to colloids. It is for this reason that the intravenous injection of no amount of blood or of any other colloid solution in which all the water is combined with colloid is followed by an increased urinary output. On the other hand, a salt solution at once leaves the body because its water is "free." The lymph remains in the lymph vessels for the same reason. (See pages 403–415.)

These facts are of importance in establishing the principles that must guide us in any attempt to increase the blood pressure in patients suffering from an abnormally low one. The salt solutions injected into the blood vessels by way of increasing the pressure produce their good effects but temporarily because they consist of free water which leaves the body in the secretions or is sucked out of the blood vessels into the tissues. Only transfusion mixtures in which all the water is held in colloid combination can remain in the blood vessels. It is for this reason that transfusion with blood, blood serum, hydrocele fluid, ascitic fluid or a properly prepared gelatin solution yields good and lasting results. (See pages 415–422.)

How these principles have been utilized by various workers dealing with the practical problem of shock during the Great War is outlined. (See pages 423–426.)

PART FIVE

The normal, abnormally low and abnormally high water content of cells discussed by the biologists under the terms turgor, plasmolysis and plasmoptysis are next considered, and it is indicated how these phenomena as observed in spermatozoa, epithelial cells, white blood corpuscles, muscle and other cells and tissues when subjected to the action of acids, alkalies, salts and various non-electrolytes, are more easily explained through colloid-chemistry than through the older, more popular "osmotic" notions of water absorption. (See pages 429–438.)

The problem of hemolysis receives special consideration. It is shown that changes in the size of the red blood corpuscles and the escape of hemoglobin from them are frequently associated, but not identical, processes. The changes in size follow the laws of water absorption by simple colloids, the loss of color entirely different ones. The hemoglobin and the stroma of the corpuscle are united as an adsorption compound similar in nature to the combination existing between certain colloids and dyes. The parallelism between the laws governing the absorption of water and the loss of color by carmine-stained fibrin and the absorption of water and loss of color by red corpuscles is described in detail. (See pages 438–445.)

The source of the energy for growth, which is defined as increase in volume, is found in the swelling of the colloids produced in the process of growth. The mechanism by which curvatures are produced in consequence of the directive action of various external stimuli (tropisms due to light, heat, chemicals, electricity, water) is found in the unequal swelling of hydrophilic colloids, and it is indicated how many of these phenomena can be mimicked in the laboratory by the use of cylinders, strips and leaves of gelatin irregularly painted with acids, alkalies and other substances. (See pages 446–451.)

Catgut strings when subjected to the action of acids shorten. This shortening is due to an absorption of water. They lose their water and lengthen again when the acid is washed out or

neutralized. Various salts affect this contraction and relaxation. entirely similarly to the way in which they affect the absorption and giving off of water by various protein colloids. When such contractions are registered upon a drum, a series of curves is obtained identical with those produced by the contraction and relaxation of muscle. By varying the conditions surrounding the catgut the phenomena of rigor, fatigue, staircase, residual contraction, increased tone and tetanus can be mimicked. The analogy between the contraction and relaxation of catgut and the contraction and relaxation of muscle under similar circumstances leads to the conception that the muscle contraction represents a problem in colloid-chemistry, the contraction representing a swelling and shortening of the muscle fibrils under the influence of a temporary acid production; the relaxation, the neutralization of this acid with loss of water. The contributions of various authors toward the establishment of such a colloid-chemical theory are reviewed. (See pages 451–470.)

PART SIX

The term nephritis is used to cover that symptom complex which clinically is characterized by the appearance of casts and albumin in the urine, by certain morphological changes in the kidney, by changes in the amount of water given off, by changes in the amount of dissolved substances secreted in the urine and by the associated œdema, increased blood pressure and cardiac hypertrophy. The changes that characterize nephritis are colloid-chemical in nature and due to a common cause — the abnormal production or accumulation of acid and of substances which in their action upon colloids behave like acid in the cells of the kidney. To the action of these upon the colloid structures that make up the kidney are due the albuminuria, the specific morphological changes noted in the kidneys, the associated production of casts, the quantitative variations in the amount of urine secreted, the quantitative variations in the amounts of dissolved substances secreted, as well as the other signs of nephritis which appear in direct connection with the kidney. The alleged consequences of kidney disease such as œdema, high blood pressure, uremia, etc., are not consequences, but accompanying signs and symptoms which demand separate

discussion and analysis. Proofs of the correctness of these contentions follow two lines:

1. A consideration of the chemical factors which bring about the colloid changes.

2. A consideration of the colloid changes themselves. (See pages 473–475.)

As under the first heading, an abnormal production and accumulation of acid is considered of chief importance, it receives main emphasis. The proof that an abnormal production or accumulation of acid occurs in the kidney in every case of nephritis comes from three directions:

1. The acidity of the urine determined either by titration or by measurement of its hydrogen ion content is constantly high.

2. The blood shows a so-called decreased alkalinity.

3. Dyes of various kinds which show a characteristic color only when the acid content of a tissue is sufficiently high and which show no color when injected into normal tissues, stain the kidneys when the signs and symptoms of a nephritis are present. (See pages 475–488.)

On the other hand, it can be shown that any method which leads to an increased production or accumulation of acid in the kidney is a means of producing nephritis. Direct introduction of sufficient acid into the organism is followed by the appearance of casts and albumin in the urine and a diminished output of water. When the acid is produced by the organism itself, as in hard muscular work (long marches, athletic games, running matches, etc.) these signs again follow. The real reason why the signs of a nephritis appear after hard muscular work is because the lactic acid produced in the muscles and necessary for their contraction is not oxidized as fast as formed. In other words under such "normal" circumstances there occurs a sufficient accumulation of acid in the body and in the kidney specifically to give rise to albumin and casts in the urine if the normal supply of oxygen to the tissues is reduced. Under pathological circumstances a reduction in oxygen supply comes to pass in heart disease, respiratory disease, the anemias, carbon monoxid poisoning, etc., and this explains why albumin, casts, etc., appear in such cases.

Under all these circumstances the original conditions leading to the nephritis lie entirely outside the kidney. Direct inter-

ference with the oxygen supply to the kidney itself, as through pressure upon its blood vessels, arterio-sclerosis, etc., is followed by a local production or accumulation of acid in this organ and by the signs of nephritis. A final way of causing an abnormal production or accumulation of acid is by interfering with the power of the kidney to utilize oxygen even though this is supplied in sufficient amount. The metallic salts, the alkaloids, the anesthetics and other poisons belong to this group. The albuminuria of the newborn and that occasioned by salt starvation and excessive consumption of water receive consideration. (See pages 488–502.)

Incidentally, it will be observed that the argument regarding the nature and cause of nephritis is much the same as that previously given for the nature and cause of œdema. Actually, nephritis is in good part an œdema of the kidney.

As noted in discussing œdema, other substances besides acids, notably the alkalies, urea, pyridin and certain amins are capable of increasing the hydration capacity as well as the solution of proteins. Since swelling and solution of its proteins characterize the nephritic kidney we are not surprised to find these same substances capable of inducing a nephritis. In cases of alkali poisoning, or when alkali is introduced intravenously into animals, all the signs and symptoms of a nephritis develop. (See pages 502–504.)

How now does such a single factor as an abnormal production and accumulation of acid in the kidney lead to the signs and symptoms of a nephritis? Acid acting upon protein makes it not only swell, but go into solution. The albuminuria of nephritis not traceable to gross lesions, as to bleeding, to diapedesis of red or to migration of white blood corpuscles, etc., is due to such a solution of the kidney proteins in the urine. The relation between the so-called swelling and the solution of a protein receives separate consideration. While frequently associated processes, they are essentially different. What they seem to represent from a theoretical point of view is taken up. (See pages 504–531.)

Before discussing the mechanism by which each of the different morphological changes characteristic of nephritis is brought about, it is necessary to come to an understanding of what is the relation to each other of the different types of nephritis which we recognize clinically, and how these are correlated with anatom-

ical findings. There is only one kind of nephritis, parenchymatous nephritis, but this may affect all the kidney or only spots in it. When the former occurs, as after an intoxication which involves the whole kidney, we speak of a generalized parenchymatous nephritis. Anatomically this is a large swollen kidney, while clinically it is characterized by much albumin, many casts and little or no urinary secretion. If the patient does not die, one of two things may happen so far as the kidneys are concerned. They may recover entirely or pieces in them may die, be absorbed, and naught but a scar remain to mark the place of death. If this happens a secondarily contracted kidney ("small red kidney") results. As long as one-quarter of the total kidney substance is saved it suffices for the patient's needs, and he may live and die with this without ever being aware of his state. Nor can his state be recognized clinically. (See pages 532–534.)

Depending upon the factors responsible for it, a spotty parenchymatous nephritis may also recover or the involved areas die. If the latter occurs, replacement by connective tissue again follows, and the "small red kidney," which, as morphologists, we call chronic interstitial nephritis, again results. (See pages 534–535.)

The mechanism, however, by which a spotty nephritis is brought about is usually totally different from that which brings about a generalized nephritis. A poison circulating in the blood affects for the most part the whole kidney at once and uniformly. For the focal lesions there must be focally acting causes. Most commonly these are found in the changes of blood-vessel disease which lead to a defective blood supply with destruction and death of one piece after another of the kidney. As the connective tissue which replaces the lost areas has been very generally regarded as the cause of the necrosis instead of consequent thereupon, these kidneys are called primarily contracted kidneys. As the small areas of kidney substance become involved there appear a few casts and a little albumin in the urine. But since the kidney between these spots is functioning normally and since one-quarter of the total kidney substance suffices for all ordinary needs, the urinary output in such patients remains normal. As will be shown later, the high blood pressure, cardiac hypertrophy, etc., so frequently observed with this type of chronic interstitial nephritis, are not the consequences of kidney disease, but ex-

pressions of the vascular disease here held responsible for the kidney lesions. (See pages 535–538.)

Infections of the kidney are not ordinarily considered with the nephritides, but they might as well be. In the infections the poison is simply produced within the kidney itself instead of being carried into it from elsewhere in the body. Depending upon the amount of kidney involved, such infections may give rise to either local or generalized nephritides, accompanied in the former case by few casts, little albumin and a normal water output, in the latter by the reverse. (See page 538.)

The remaining portions of healthy kidney substance constituting the small red kidney and anatomically diagnosed as chronic interstitial nephritis, whether secondary to a generalized parenchymatous nephritis or consequent upon blood vessel disease, may at any time and for various reasons become the seat of a generalized parenchymatous nephritis. Most commonly the heart fails. When this happens, the normal or increased urinary output with few casts and little albumin gives way to a diminished output with many casts and much albumin. (See pages 538–539.)

The portions of a kidney involved in nephritis show:

1. An increase in size.

2. A loss in normal color due to the appearance of granules in the affected cells.

3. The appearance of blood corpuscles extravascularly.

4. Evidences of a falling apart of the kidney leading to the formation of casts. (See pages 539–540.)

The increase in size is due to a swelling of the kidney colloids under the influence of the abnormal production and accumulation of acid. The change in color is due to the precipitation under the same circumstances of a second colloid of the nature of casein. The two together constitute "cloudy swelling." (See pages 540–554.)

The bleeding from the kidney in nephritis is in part due to rupture of the blood vessels, in part to diapedesis. The mechanism of diapedesis is discussed. The tissues ordinarily are sufficiently stiff to prevent the red blood corpuscles from sinking into them. After absorbing water under the influence of an acid they become less rigid (their viscosity is decreased) and the corpuscles are now able to penetrate them. The process of diapedesis can be mimicked by allowing mercury drops to

move in all directions through a solid gelatin. (See pages 555–559.)

When the surface of a fresh kidney is scraped one obtains only a granular detritus consisting of broken cells, but if the kidney is treated with a dilute acid or is simply subjected to the action of such as are produced post-mortem, it falls apart into its constituent elements, the cement substance dissolving first, while the epithelial cells stick together and slip out of the tubules as casts. The casts are originally epithelial, but become granular as the action of acid upon them is prolonged. When the concentration of the acid is increased the casts become hyaline. By proper regulation of acid and salt content the hyaline casts may be reconverted into granular casts. The danger is pointed out of drawing too large clinical conclusions from the character of the casts found in the urine, which within its ordinary limits of acidity, salt concentration, etc., can so markedly change them. (See pages 560–566.)

To meet the criticism that the swelling and solution of the body proteins as observed in œdema and nephritis cannot occur in the living body under the influence of various acids because the body cells contain buffer salts (like phosphates and carbonates) experiments are introduced on the swelling and solution of gelatin and fibrin in various so-called buffer mixtures. It is shown that gelatin immersed in different concentrations of the primary, binary and ternary salts of phosphoric, citric or carbonic acids swells not only with the salt but with its concentration. The absorption of water is detailed by gelatin plates lying in phosphate and citrate mixtures, varying from the extreme of the pure acid on the one side, through the mono-, di- and trisodium salts of these acids to pure sodium hydroxid on the other. Irrespective of the manner in which these mixtures are prepared (whether by progressive substitution of one salt for another through the addition of the requisite acid to an alkali, through the addition of alkali to the proper acid, through the addition of either acid or alkali to a given salt) it is found, when the amount of water absorbed is plotted on the vertical and change in composition of the mixture on the horizontal, that the result yields a V-shaped or U-shaped curve. From a minimal point in the middle of this curve there is a progressive increase in water absorption to the left or to the right as the acid content or alkali content of the mixture is increased. What

has been said of phosphate and citrate mixtures holds also for carbonate mixtures. (See pages 567–596.)

A study of the liquefaction or "solution" of gelatin in these same polybasic acids and their salts shows that solid gels may be obtained only in the lowermost portions of the V- or U-shaped curves,—that this protein, in other words, tends to soften, to liquefy and to go into solution as we pass from a middle point in these buffer mixtures in the direction of either acid or alkali. (See pages 596–602.)

A study of the swelling of fibrin in polybasic acids and their salts brings out the same general truths. The findings taken together are held to be applicable to the problem of water absorption by protoplasm and its "solution" and to sustain the old contention that even in the presence of buffer salts there is an increase in water absorption (increased turgor or œdema) and an increased tendency to go into solution (albuminuria, etc.) with every increase in acid (or alkali) content of the protein colloids found in the involved cell, organ or organism above a given low point. (See pages 602–614.)

Many of the clinical manifestations observed in patients with kidney disease are considered consequences of the impairment of kidney function. While there are consequences to loss of kidney function, those clinically regarded as such almost without exception do not belong in this group. Blood vessel disease, high blood pressure and cardiac hypertrophy are not secondary to loss of kidney function. The primary disturbance in chronic interstitial nephritis associated with vascular disease and changes in the heart is the vascular disease, and the changes in the kidneys, heart and other organs are secondary to it. This can be proved both from clinical observation and experiment. The worst cases of nephritis in which there is greatest loss of kidney function, as in the toxic nephritides occurring in scarlet fever, pregnancy, etc., there is no high blood pressure; nor when the kidney substance of animals is experimentally reduced to the physiological minimum do vascular disease, high blood pressure or cardiac hypertrophy develop. The primary change being blood vessel disease, it is easily understood why the other signs and symptoms must follow. In consequence of the destruction of one piece of kidney after another by the changes characteristic of vascular disease as displayed in the small blood vessels of this organ with subsequent replacement by scar tissue,

the kidney undergoes gradual diminution in size. The pieces die with the signs characteristic of parenchymatous nephritis, but because what remains of the kidney is healthy and but one-quarter is necessary to maintain life, patients with this type of chronic interstitial nephritis show no change in urinary output. (See pages 614–623.)

The hypertrophy of the heart is not consequent upon loss of kidney function, but is the result of a demand for increased work and increased power. The source of these demands resides in the changes in the blood vessels. Because of their decreased caliber an increased force is necessary to drive the blood through them, and because they are inelastic the heart is required to push the blood through them in the time of a systole alone, instead of as ordinarily in the time of a systole, plus a diastole, plus a pause. More work is therefore done and in less time. In mechanics more work in less time requires a more powerful machine, and the hypertrophy of the heart is an expression of this law in the body. (See pages 623–625.)

As it is only through the increased blood pressure that the different organs of the body are adequately supplied with blood when vascular disease is present, the high blood pressure cannot in itself be regarded as something evil, but must be looked upon as decidedly good. Except in hemorrhage, treatment which merely lowers blood pressure is of no value and often dangerous. Because of the weakened blood vessel walls, all those agencies which tend to increase blood pressure even in normal individuals should be controlled, but beyond this only that therapy has value which tries to combat the underlying cause of the increased pressure, namely, the vascular disease itself. "Hypertension" is not a clinical entity any more than is "fever" or "dropsy" and schemes for reducing it which do not consider its underlying physiology and pathology are worthless. (See pages 625–626.)

The œdema observed in some cases of nephritis, particularly in the parenchymatous types, is also not secondary to the kidney disease. Patients suddenly deprived of their renal function, as through accidental removal of an only kidney, or animals similarly treated by removal of both kidneys, develop no œdema. On the other hand, patients or animals poisoned with any of the popular "kidney poisons" like arsenic, salvarsan, uranium, etc., develop an oedema in a short time. But the generalized oedema

is not secondary to the kidney disease, but represents in the involved tissues the same type of change as that which in the kidney we call nephritis. (See pages 626–628.)

Similar clinical observations and experiments prove that the headache, vomiting, disturbances of vision, stupor, respiratory changes, coma and death, clinically regarded as signs of a "uremia," are not secondary to loss of kidney function. Nephrectomized patients or animals show no such symptoms. The alleged "uremic" symptoms are due to œdemas of various portions of the central nervous system and are caused by the same agents which are inducing the œdema elsewhere in the body, including the kidney. (See pages 628–629.)

A reinterpretation of the clinical manifestations associated with nephritis is attempted on the basis of these facts. (See pages 629–634.)

Since vascular disease is regarded as the cause rather than the consequence of kidney disease, its etiology is discussed. The pathological changes observed in the blood vessels in vascular disease are focal in type in even the most advanced cases. The whole of the media, or the whole of the intima of an aorta, for example, is never involved. A generalized intoxication cannot, therefore, underlie it. To get the focal lesions we must have focal causes, and infectious emboli are undoubtedly to be regarded as the underlying cause. The emboli lodge in the smaller blood vessels and thus give rise to the local necroses observed in the kidney, retina, brain, etc. When they lodge in the small blood vessels supplying the coats of the larger ones (as in the aorta) the patchy spots of softening, absorption, connective tissue overgrowth, and calcification characteristic of "atheroma" and arteriosclerosis follow. On this basis the importance of looking for sources of infection in patients with vascular disease is emphasized. (See pages 634–636.)

Disturbances in secretion in nephritis are of two types, those affecting the output of water and those affecting the output of dissolved substances. (See pages 636–638.)

The introduction of acid into the kidney by any means whatsoever is followed by a prompt decrease in urinary secretion even to the point of absolute stoppage. The same factor so largely responsible for the other signs of nephritis is therefore

responsible for this also. How this acid works is discussed. (See pages 638–640.)

The changes in the excretion of dissolved substances by the kidney must be considered under two headings. The decrease in absolute amount put out is secondary to the decrease in total amount of water secreted. The change from the normal in the relative proportions of the dissolved substances given off is secondary to changes in the solution, adsorption and chemical properties of the kidney colloids as affected by the presence in them of acid and similarly acting substances. The action of acids in thus altering the adsorption properties of protein colloids is illustrated by experiments on the taking up and giving off of dyes by fibrin. (See pages 640–648.)

Experiments are now introduced to establish further some principles of treatment. As the various salts, including sodium chlorid, were found to decrease the swelling and solution of proteins, it was to be expected, since similar changes characterize nephritis, that they would also be able to inhibit or make these subside when experimentally induced. Asphyxial nephritis, that secondary to intravenous injection of acid, and that consequent upon temporary clamping of the renal artery are studied in this regard. The decrease in urinary output, with the appearance of albumin, blood and casts in such urine as is secreted, can be overcome almost entirely if animals rendered nephritic by such experimental means are treated with various salts. Sodium chlorid is no exception to this rule. (See pages 648–665.)

To meet the objection that such suppression of the signs of nephritis can be obtained only in animals, a series of observations on the albuminuria consequent upon hard muscular work is introduced. When athletes are fed liberally on citrus fruits the albuminuria developed is decreased in severity. (See pages 665–667.)

Were we to formulate a general rule for the prophylaxis and the treatment of nephritis we should evidently have to say that this lies in an avoidance and removal as far as possible of every condition that favors the abnormal production or accumulation of acid in the kidney, or of such other substances which in their effects on tissue colloids behave like acid. After this is done, attention must be directed to combating the effects of such con-

ditions as cannot be removed. The rule to be followed may be summarized in the words: Give alkali, salts and sugar. Control the intake of water. The alkali is needed to neutralize the acid present in abnormal amount. The salts are indicated, and sodium chlorid is no exception, because the changes induced in the body colloids by the action of acids upon them are counteracted by adding salt. Dextrose or other carbohydrates are given not alone from a chemical point of view, in that an abnormal production and accumulation of acid is frequently the consequence of carbohydrate starvation, but because the sugars are peculiarly powerful in reducing certain types of increased hydration in protein not produced by acid. The water intake must be reduced to a minimum when tissues are to be dehydrated; it must be increased when "free" water is demanded for increase in secretion. (See pages 667–669.)

The importance of the diet in treatment is considered. Foods high in the mineral acids or in those organic acids (benzoic, oxalic, tartaric, etc.) which cannot be readily oxidized to carbonic acid in the body should be avoided unless special pains are taken to give with such foods an adequate supply of alkali to neutralize these acids. A protein diet yields, after oxidation in the body an excess, roughly, of 25 per cent of acid, while a vegetable and fruit diet yields under the same circumstances a 25 per cent excess of alkali. Hence the advantage of the vegetable diet over the meat diet. Practically, however, drastic restrictions in the dietary are not to be recommended. It is easier and better for the patient to be liberal with the diet, but to protect him against the effects of an excess of acid by a continuous feeding of alkali to the point where his urine is kept persistently neutral to litmus. (See pages 669–674.)

The question of water consumption in nephritis resolves itself into two parts, into the use of water in cases where nephritis is likely to arise and into its use in the established case. Normally the patient needs water in order to have free water available out of which to make urine, and since the development of a nephritis depends in the end upon an intoxication, water is needed to reduce its concentration, for intoxication depends upon concentration. The giving of water does not materially increase the work thrown on the heart as generally taught, wherefore heart disease, blood-vessel disease, etc., do not by themselves contraindicate its use.

Neither is there any scientific reason against giving water in chronic interstitial nephritis. The objections to the use of water are two: first, when the hydration capacity of the body colloids is increased, the giving of water makes possible their swelling; second, pure water in washing through the kidney washes out not only poisonous substances of which we would be rid, but also salts of various kinds which we would keep. To give the organism the benefits of water without its accompanying bad effects, we need to give along with the water properly chosen salts in sufficient amount. (See pages 674–676.)

The natural and artificial means of establishing and maintaining a proper salt concentration in the body are discussed. (See pages 676–678.)

When the gastric route alone does not suffice to get adequate amounts of alkali and salt into the organism the rectal or the intravenous route may be employed. The formulas of proper solutions to use under such circumstances are given. Never must alkaline mixtures be used subcutaneously or intramuscularly. (See pages 678–695.)

The case histories of a series of patients are given and commented upon to illustrate the practical use of the principles of treatment outlined in this volume. (See pages 696–731.)

How alkali, salt and dextrose may be used to relieve the alleged consequences of kidney disease ("uremia," vomiting of central origin, papillo-œdema, etc.) as well as other conditions in which an œdema of the affected organs constitutes a characteristic feature is emphasized. (See pages 731–734.)

Œdema as an alleged consequence of sodium chlorid retention is next discussed. Retention is not due to an inability of the kidney to eliminate chlorid, but to change in the (protein) colloids of the body, which, under the influence of an abnormal production and accumulation of acid, not only swell (become œdematous) but at the same time retain more chlorid. Experiments on gelatin and fibrin are introduced to support this contention. (See pages 734–738.)

The generalized œdema so frequently observed as an accompaniment of certain types of kidney disease needs to be treated on the same principles as the œdema of the kidney itself. All salts are indicated because they decrease this generalized œdema

as they do the swelling of the kidney itself, and sodium chlorid is no exception to the rule. (See pages 738–740.)

The accumulations of fluid in the body cavities in states of œdema represent colloid solutions in which the water is largely bound to the colloid as hydration water. They are therefore absorbed only with difficulty, and this is why when sufficiently large in amount they need to be and can be gotten rid of only by tapping. How the administration of salt and alkali while reducing the œdema of the body tissues generally may increase the accumulations of fluid in the cavities is commented upon. (See pages 740–743.)

An effort is made to explain how the salt restriction scheme of therapy practiced by many, leads to the good results reported. It is not the salt restriction, but the accompanying water restriction that does the work. By sufficiently reducing the intake of water we succeed in losing more water (by evaporation, etc.) in the unit of time than is taken in, and so all the organs of the body dry out. This at times succeeds in breaking into the vicious circles established in many organs when once they begin to swell. The swelling compresses their blood supply and thus aggravates their already precarious state. Dehydration of the organ through water starvation may suffice to save it. It is pointed out, however, that by obtaining such dehydration through administration of properly chosen salts with water instead of through water starvation, we gain the advantage for our patient of having water available to float off his poisonous products. (See pages 743–745.)

The meaning of the signs and symptoms displayed by patients, the victims of nephritis, and their prognostic value are taken up, and the correlation between urinary findings and the clinical manifestations originating in organs other than the kidney is made. (See pages 746–757.)

The physiological principles to be borne in mind in any attempt to develop an efficiency test for an organ are considered. Because of the great reserve available in nearly all of them they continue to show a normal function as long as more than a physiologically necessary minimum remains preserved. Three-quarters to seven-eighths of the normal functional capacity of an organ may be lost before the organism as a whole shows the effects of it or before it can be discovered by functional tests. Even then

the test must be heightened to the point of straining what remains before the loss becomes apparent. These considerations hold for the kidney. The functional capacity of the kidney is best tested by its power to eliminate water. I have never seen a kidney that would secrete water which would not also secrete all dissolved substances. Tests dependent upon an elimination of dissolved substances are fraught with greater possibilities for error and are therefore less satisfactory. As long as one-quarter (more probably one-eighth) of the total kidney function is preserved all such tests yield normal figures. Animals in which three-quarters of the total kidney substance has been removed excrete water and all dissolved substances as do normal animals. When less than one-quarter (or more probably one-eighth) of the total kidney substance is functioning a diminished output of water and of certain dissolved substances becomes evident, but when such extreme states of renal insufficiency are experimentally produced or encountered clinically elaborate tests are not necessary to bring them to light. Efficiency tests are of greatest service for the discovery of unilateral kidney lesions. The teaching that successful prognostications regarding the onset of "uremia," etc., can be made on the basis of kidney efficiency tests, needs to be examined critically, for most of such alleged consequences of kidney disease are not consequences. (See pages 757–765.)

Since an abnormal production or accumulation of acid in the kidney is so largely responsible for the development of the signs and symptoms of nephritis, the importance of following the acidity of the urine is emphasized. The meanings of titration acidity and of hydrogen ion acidity are defined. The determination of either or of both furnishes valuable data in the clinical control of every case of nephritis, but neither can alone serve as an index to the severity of the intoxication occurring in the kidney. How the physician may use simple indicators in the urine by way of determining roughly its hydrogen ion acidity and the meaning of such determinations is explained. (See pages 765–778.

It is characteristic of animals when subjected to intoxication with acid to draw first upon their supply of fixed bases to neutralize the acid. When these have been largely exhausted the carnivora have a second method of meeting the acid intoxication, namely,

by the production of ammonia. An absolute or relative increase in the ammonia output in the urine (or other secretion from the body) therefore becomes evidence for and a quantitative guide to the degree of acid intoxication. The usefulness of ammonia determinations in nephritis is therefore emphasized. (See pages 778–783.)

The section closes by pointing out how a diagnosis of nephritis has in itself but little meaning, in that after this has been made it is ever necessary to say why the nephritis has come to pass. As the conditions leading to or likely to lead to the signs and symptoms of nephritis are largely known, the great importance of prophylactic measures is emphasized. (See pages 783–792.)

PART SEVEN

Glaucoma from a pathological standpoint represents one of the local œdemas, and from a clinical point of view all its signs and symptoms are referable to the increased intraocular pressure resulting from the œdema. An eye becomes glaucomatous not because water is forced into it, but because it suffers changes which make it suck up an increased amount. The eye is built up of a series of colloids which normally have a certain hydration capacity. Anything which in the body is capable of increasing this hydration capacity leads to a swelling of the eye and constitutes therefore a cause of glaucoma. As in other forms of œdema, evidences may be found in cases of glaucoma for an abnormal production or accumulation of acids in the eye and of substances which in their action upon colloids behave like acids. (See pages 795–797.)

As the abnormally high hydration of the ocular colloids which characterizes glaucoma may be reduced through various salts, so can clinical cases of glaucoma be given relief from symptoms by the subconjunctival injection of properly selected salts such as sodium citrate. (See pages 797–799.)

The problem of glaucoma and its treatment is identical with the problem of nephritis, and exactly as we err in the treatment of nephritis when we consider only the kidney, so do we go wrong when in glaucoma we consider only the eye. Starvation, an excessive protein diet, hard muscular and mental work, excessive

consumption of sour wines, various intoxications (anesthetics, alcohol and arsenic), the infections, the severe anemias, arteriosclerosis, uncompensated heart lesions, exposure to cold, etc., are all associated with an abnormal production of acid in the body, and constitute in consequence potent factors in the precipitation of the glaucomatous attack. These must be recognized and removed if we expect the attack to subside. If they cannot be removed, then we need to meet their consequences, and since we deal here with factors affecting the whole patient we must treat him. For this reason alkali, salts, dextrose and a controlled water intake are indicated in the same way and for the same reasons as in nephritis. (See pages 799–802.)

The prognosis in glaucoma depends entirely upon the nature of the factors appearing in its etiology. A diagnosis of "glaucoma" is as complete as one of "dropsy." When the swelling is due to a transient intoxication, or to temporarily acting infections, mere reduction of tension by any means whatsoever, whether surgical or medical, can easily lead to brilliant results and permanent relief, but when irremovable causes such as blood vessel disease are responsible for the glaucoma—by far its commonest cause in older individuals—no scheme of treatment which ignores the blood vessel disease and which merely centers attention upon the eye can yield anything but temporary and ultimately disappointing results. (See pages 802–806.)

The nature of the corneal opacities and the cloudiness of the clear media so often observed in glaucoma and certain other pathological states is discussed. They are not due to œdema, but represent precipitations of protein of the nature of casein. The "clouding" thus caused by the precipitation of one type of colloid while another is swelling, together make glaucoma but another example of the widely observed "cloudy swelling" of the pathologists. (See pages 806–810.)

A paragraph asking that those who feel tempted to make clinical use of any of the therapeutic methods discussed in the volume feel tempted also to study the scientific principles upon which they are based in order that misunderstanding and disappointment through improper application of the suggested remedial measures may be prevented, closes the volume. (See pages 810–811.)

PART EIGHT

The importance of foci of infection in and about the body for the production of the signs and symptoms of nephritis and its complications leads to a discussion of the general pathology and bacteriology of focal infection. To illustrate what needs to be done clinically for the control of all such points of infection, the problem of infection in and about the teeth is taken up in detail. The significance of the teeth as living tissues is stressed, the physiology of their maintenance is discussed and the pathology of their infection is reduced to that of the general pathology of infection in bones and joints. On such basis the principles are then enunciated which are considered the right ones for their proper medical and surgical care. (See pages 815–851.)

A clinical lecture is set down to illustrate how in practice the concepts of the nature and the cause of nephritis as set forth in this volume may be used for the classification, diagnosis, prognosis and treatment of patients afflicted with kidney disease and its alleged consequences. (See pages 852–892.)

PART TWO

ABSORPTION AND SECRETION IN INDIVIDUAL CELLS AND TISSUES

PART TWO

ABSORPTION AND SECRETION IN INDIVIDUAL CELLS AND TISSUES

I

THE PROBLEM

When, in the routine of our day's work, we are brought face to face with so practical a matter as the treatment of a patient suffering with glaucoma, or from the convulsions of uremia, or from an anuria, our behavior, if it is not a blind following of empirically transmitted teachings, is determined by what we think of the nature and the cause of these deviations from the normal. In good part we deal in these illustrations with an œdema of the affected organs—of the eye, of the brain, of the kidney—and so our treatment becomes but a specialized expression of what we think regarding the nature and cause of œdema in general.

But this problem of œdema—the problem of the presence of abnormally large amounts of water in tissues and tissue spaces—is in itself only a phase of a still greater problem: Why does protoplasm hold any water at all, and why does it hold under normal circumstances so nearly constant an amount?

It is easily seen why an interest in œdema or in such special expressions thereof as glaucoma, uremia or nephritis should have overshadowed the greater and really simpler problem, for all these have a human interest that is entirely lacking to the question of why protoplasm generally holds water. That attempts should in consequence have been made to answer the question of œdema first is not surprising. The ways and means adopted

may, however, well serve as an example of the short-cut methods which clinicians and pathologists have only too often adopted in order to obtain light, and with disastrous results. Since œdema constitutes a pathological state of interest chiefly in man, various hypotheses were formulated to account for the condition on the basis of his complex anatomy—such, for instance, as his blood and lymph circulatory systems; and when experiments on the higher animals failed to bring the corroborating evidence which should convert the shadowy hypothesis into the healthy theory, recourse was had to the still more shadowy properties of " living " cells. To this day the accepted explanation of œdema remains an ill-defined mixture of the physical concepts of pressure and filtration with the mysterious forces of "living" matter.

A little thought will show that variations in the amount of water held by cells and tissues occur in a great variety of animals and plants. To cite but a single example, and one common to both plants and animals, mention may be made of the long studied phenomena of normal, increased and decreased water content in cells which are discussed under the terms turgor plasmoptysis and plasmolysis. Isolated animal and plant cells have normally a certain water content. Under a variety of circumstances they may be made to absorb more. These are " œdemas " as true as any ever observed in man, or produced experimentally in dog or rabbit. Such reflection should by itself have created suspicion against any conception of œdema which demands for its production circulatory systems or any structures not common to *all* protoplasm, vegetable as well as animal.

It will not seem strange therefore that the best contributions toward the solution of the problem of the ways and means by which cells and tissues absorb water have in recent years really come through the plant physiologists. Not led into erroneous paths through the presence of circulatory systems at all similar to those found in the higher animals, the plant physiologists early sought the explanation of the variations in the amount of water held by the plant tissues in the cells themselves. As we shall see shortly, this is where the problem belongs, and the attempts of later years to make differences in osmotic pressure responsible for the movement and storage of water in animal cells as well as in plant cells under normal and pathological con-

ditions cannot be too highly commended. While the theory of osmotic pressure is incapable of accounting for more than a very small portion of the phenomena observed—even in plants—the great value of an attempt to explain variations in the water content of animal and plant tissues on a healthy physico-chemical basis cannot be questioned.

To a consideration of the various hypotheses and theories that have been proposed to account for the normal water content of cells and for the abnormally high water content which the plant physiologists discuss under plasmoptysis, the pathologists under œdema, the clinicians under a variety of terms, we shall have occasion to return later. Here we would only emphasize the fact that all these diversified phenomena bear a close relation to each other and need to be discussed together. The clinician meeting his medical problem has common interest with the pathologist; the pathologist in turn can discuss his more abstract notions of œdema only as he considers the physiologist and his ideas of normal water absorption. This will explain why we need in this volume to begin with a discussion of fundamental physiological principles. And at all times subsequently must we find it easy to pass from the extremes of pathology back to physiology, or *vice versa*.

The unit for consideration in physiology, and so in pathology and applied medicine, remains the cell. As practical men we are likely to lose sight of this fact or to take exception to it, yet the most practical will heed the physiology of the individual cell most. Even the highly specialized functions of groups of cells or of organs in a complex individual rarely represent more than exaggerations of functions common to all cells. This is why this volume begins with and constantly reverts to the behavior of the individual cell. To be familiar with the effect of various external conditions upon the general behavior of the individual cell is to be familiar with the behavior of these same conditions upon groups of cells. When such groups of cells (an organ) are part of and determine the behavior of yet other groups of cells in a complex organism, familiarity with the action of these external conditions upon the isolated groups of cells becomes synonymous with a knowledge of the action of these external conditions upon the organism as a whole. An understanding of the most specialized therapeutic procedure is almost invariably

dependent upon such a knowledge of the cell. We shall find many an illustration of this as we proceed.

With this let us turn to our specific problem of water absorption by the living cell under physiological and pathological circumstances. Since I consider the colloids of the tissues and their state as of chief importance in this matter, a review of the properties of colloids with particular reference to their behavior toward water is first in order.

II

THE ABSORPTION OF WATER BY COLLOIDS

1. Remarks on Colloids: Nomenclature

While theories regarding the nature of the colloid state do not in any way affect the argument of the succeeding pages, brief reference to them as evolved by the work of various students of the problem during the past several decades may help to clarify what must otherwise be carried in the mind in more nebulous form.[1]

§ 1

It is now more than fifty years since Thomas Graham[2] recognized that chemical substances differ greatly in the rate with which they diffuse through solvents of various kinds. On the basis of this observation he made a distinction between those which diffuse but slowly and those which diffuse rapidly. As the former are for the most part amorphous, and since ordinary glue (κόλλα) is an example of this class, he called them *colloids*. The group that diffuse readily he called *crystalloids*, for such beautifully crystal-

[1] Surveys of the field of colloid chemistry are now available in several splendid texts which must be consulted for details beyond the confines of this volume. See especially Wolfgang Ostwald: Theoretical and Applied Colloid Chemistry, translated by Martin H. Fischer, New York (1917); Handbook of Colloid Chemistry, translated by Martin H. Fischer, 2d Ed., Phila. (1919); Richard Zsigmondy and Ellwood B. Spear: Chemistry of Colloids, New York (1917); Jerome Alexander: Colloid Chemistry, New York (1919); H. Bechhold: Colloids in Biology and Medicine, translated by J. G. M. Bullowa, New York (1919).

[2] Thomas Graham: Phil. Trans., 183 (1861); Liebig's Annalen, **121**, 13 (1862).

line substances as cane sugar, ordinary salt and urea are found in it. GRAHAM noted also a second difference between his colloids and the crystalloids. While the latter, when enclosed in a fish bladder or parchment paper tube passed readily through such structures into a surrounding medium of, say, pure water, the colloids did not do so. This is the principle which underlies *dialysis*. When, in other words, a mixture of colloids and crystalloids were together subjected to dialysis only the crystalloids diffused out of the mixture and through the dialyzing membrane,—there occurred a separation or what GRAHAM termed an "analysis" of the mixture by dialysis.

Since GRAHAM's studies we have become familiar with further characteristics of colloids and crystalloids. Crystalloids are ordinarily stated to form "true" solutions. This means that when such a substance as common salt is dissolved in water there is nothing about the finished mixture which does not show it to be *homogeneous*. Light waves, for example, pass through it as though it were of exactly the same composition throughout. The typical colloids behave in quite a different fashion. They are said to form "pseudo-solutions" and even relatively superficial tests may suffice to show that they are *heterogeneous* in composition. While still "solutions" in ordinary parlance they are less apt, when viewed by ordinary light, to be "clear." They are commonly opalescent or distinctly turbid, indicating that light waves no longer pass through them without encountering greater difficulties in some spots than in others. More technically put, there are existent in these pseudo-solutions *phases* possessed of different properties. But such characteristics tend to put these systems into the physicist's realm of the "suspensions."

Of other distinctions between colloids and crystalloids modern analysis has shown that solutions of crystalloids show an osmotic pressure, a lowering of the freezing point and an elevation of the boiling point proportional to the number of particles of dissolved substance contained in the unit volume of solvent. The most typical colloids show practically no such relations. These differences are commonly paralleled with the molecular weights of the substances representative of each of the two groups, which in the case of the most pronouncedly colloid bodies is often said to be measurable in thousands, while a hundred or two covers the weight of even the more complex organic crystalloids.

Such facts made it long appear as though colloids might be correctly defined as pseudo-solutions or suspensions of amorphous, non-diffusing, non-dialyzing materials of high molecular weight, showing little inclination to yield systems governed by the ordinary laws of dilute solutions. When systems were encountered which did show such behavior we did in fact usually find ourselves face to face with colloids and yet what has been written is not sufficient to cover all cases. All the distinctions thus far drawn between colloids and crystalloids are really attempts at the classification of *substances*, and several and serious attempts were actually made to catalog compounds as either colloids or crystalloids. But time showed their inadequacy, for substances definitely colloid under certain circumstances could, under others, be obtained in crystalloid form and vice versa. Hemoglobin or albumin, for example, ordinarily characteristically colloid were obtained in crystalline form while such comparatively simple bodies as silicic and tungstic acids and the various metal hydroxids, were found in the group of the most representative colloids. Such facts sufficed to show that *no hard and fast line could be drawn between the colloids and the crystalloids.* In fact, as colloid-chemical investigation proceeded it became more and more evident that *any substance could be obtained in colloid form.*[1] This discovery necessitated a complete change in our concept of the term. *Colloids are no longer to be thought of as substances but as materials in a certain state; the term colloid is not a noun but an adjective.*

Modern study has shown that colloid chemistry occupies the middle ground between that of the chemist who deals with substances in true solution and that of the physicist who works with matter in mass, as in coarse suspensions. A solution, to the chemist, is a mixture of one material in a second with the degree of subdivision of the first in the second carried so far as to yield only particles of molecular or smaller size (the molecules, ions or electrons found in an ordinary "true" solution of sand in water, for example). On the other hand, a suspension, to the physicist, is a mixture in which he distinguishes fairly easily, as by optical methods, the subdivided material from that in which it is subdivided. He is able, for instance, not only to recognize microscopically the particles of sand in a sand-water mixture but he can

[1] P. P. von Weimarn: Kolloid-Zeitschr., 2, 76 (1907); *ibid.*, 5, 62, 117, 151, 212 (1909).

separate these from the water by allowing the mixture to stand. *Colloid solutions lie between these two extremes. They are subdivisions or dispersions of one material in a second with the degree of subdivision coarser than molecular and yet not so coarse as to lie within the physical realm of easy microscopic visibility. While the limits chosen are arbitrary* (since there exist no *abrupt* transitions from true solutions to colloids, nor from these to the suspensions) *the subdivided materials have on this basis a diameter coarser than 1/1000000 millimeter and finer than 1/10000 millimeter.*[1]

This relationship of colloid chemistry to the realms of the molecular chemist and of the physicist may be illustrated in diagrammatic fashion by such a drawing as Fig. 1. The shaded fragment of a circle marked *A* is representative of a micrococcus. Though on the edge of easy microscopic visibility it is nevertheless very coarse as compared with even the coarsest particles observable in a colloid solution. The circles marked *B* (drawn to the same scale) illustrate the size of particles of colloid gold which are falling out of "solution" and which are therefore approaching the realm of the physicist and his coarse suspensions. The smaller circles in the region marked *colloid* show the size of particles which remain suspended. While the larger of these cannot be seen as separate particles with the ordinary microscope they can still be recognized ultramicroscopically. The smallest, however, escape even such analysis and need to be demonstrated by still subtler means. The particles marked *C* are of a diameter which has been calculated as correct for the largest molecules. On the scale chosen for the diagram these circles might represent hemoglobin molecules. But hemoglobin, it will be remembered, was the substance about which there was dispute above as to whether, on solution in water, it yielded a "true" solution or not. Its position on the crossing line from the colloid solutions to the "true" or molecular solutions shows why this is the case. The coarser black dots in the realm marked *molecular* illustrate the calculated size of chloroform molecules; the fine black dots that of hydrogen molecules. Obviously the molecular fragments which are known as ions, atoms and electrons must lie still further to the right in the general diagram.

[1] See Richard Zsigmondy: Zur Erkenntnis der Kolloide, 122, Jena (1905); Richard Zsigmondy and E. B. Spear: Chemistry of Colloids, 19, New York (1917); Wolfgang Ostwald: Kolloid-Zeitschr., 1, 291 (1907); Theoretical and Applied Colloid Chemistry, translated by Martin H. Fischer, 17–21, New York (1917).

This definition of the colloids as divided or dispersed systems with the dispersed particles possessed of certain sizes has, however,

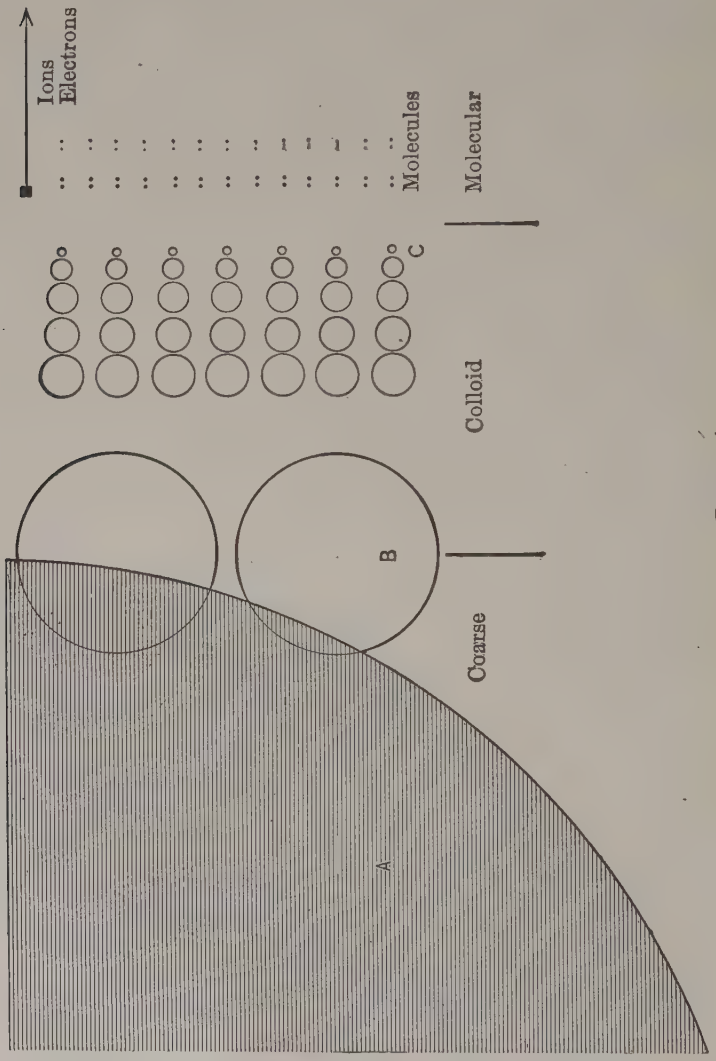


FIGURE 1.

necessitated and brought with it a widening of our whole point of view regarding such systems. The general argument as outlined above has been illustrated by referring to quartz subdivided in water or metallic gold in water, in other words, by systems repre-

sented by the dispersion of a solid in a liquid. It is obvious, however, that from the three physical states of matter, gaseous, liquid and solid, many other such "dispersoids" may be compounded and as follows:[1]

gas in gas	*gas in liquid* (foam)	*gas in solid* (meerschaum)
liquid in gas (steam)	*liquid in liquid* (emulsion)	*liquid in solid* (opal)
solid in gas (smoke)	*solid in liquid* (suspension)	*solid in solid* (certain semi-precious stones)

Whenever a material in any one of the three physical states may be thus subdivided in any second and this with a degree of dispersion which is coarser than molecular and not yet so coarse as to come within the realm studied by the physicist we are face to face with a colloid system. Of the nine possible combinations listed above, eight have been realized in colloid form (the dispersion of a gas within a gas being possible only in molecular or supermolecular form). Familiar illustrations of the types of systems resulting when matter in one form is dispersed in any other, are given in parentheses after the classifications. While illustrations of each of the systems may be found in biological material under various physiological and pathological circumstances those of greatest importance consist of mixtures of liquid with liquid and of solid with liquid. In the future therefore when unmodified reference is made to a colloid or a colloid system those which come under these chief heads are the ones generally held in mind.

§ 2

Long before the definition of the colloid state had attained the precision outlined in the above paragraphs it was noted that indisputably colloid systems differed sharply among themselves in their characteristics. The first to try to systematize these differences was A. A. Noyes,[2] who early distinguished between those colloids which are "viscous, gelatinizing and not readily coagulated by salts" and those which are "non-viscous, non-gelatinizing and readily coagulated by salts." To the former belong, for example,

[1] Wolfgang Ostwald: Kolloid-Zeitschr., **1**, 291 and 331 (1907); Theoretical and Applied Colloid Chemistry, translated by Martin H. Fischer, 40, New York (1917); Handbook of Colloid Chemistry, translated by Martin H. Fischer, 2d Ed., 42, Phila. (1919).

[2] A. A. Noyes: Jour. Am. Chem. Soc., **27**, 85 (1905.)

the colloid solutions of gelatin, soap or dextrin in water, while with the latter may be mentioned the colloid solutions of gold and quartz in water, already touched upon above.

The essential difference between the two groups resides in the relation which the colloidally dispersed material bears to the solvent. This relationship is close in the case of the colloids of the first-named type and largely absent in the case of the second. For this reason the former are also known as *lyophilic* colloids, or, when water is the solvent, *hydrophilic* colloids; the latter as *lyophobic* or *hydrophobic* colloids (J. PERRIN[1] and H. FREUNDLICH[2]).

WOLFGANG OSTWALD[3] who has done so much for the proper definition and classification of the colloids distinguishes between those which are produced when a liquid is dispersed in a liquid (the *emulsion colloids* or *emulsoids*) and those produced when a solid is divided into a liquid (the *suspension colloids* or *suspensoids*). Because it is harder to separate a liquid from a liquid than a solid from a liquid, a system built up of the former will show a greater viscosity, stability, etc., than a system of the second type. The attempt has often been made to make the emulsion colloids of OSTWALD synonymous with NOYES' first group or PERRIN's hydrophilic colloids and the suspension colloids of OSTWALD with NOYES' second group and PERRIN's hydrophobic colloids. OSTWALD[4] has himself emphasized the error of this.

Systems of the undoubted composition liquid plus liquid are not always lyophilic and systems of the composition solid plus liquid are not always lyophobic. Liquid fat, for example, subdivided in water yields a lyophobic system, while solid sodium stearate in water, alcohol or aldehyd yields a lyophilic colloid. *A lyophobic colloid results whenever the colloidally dispersed phase is not a solvent for the solvent; a lyophilic colloid when the dispersed material is such a solvent.* Because fat is not a solvent for water the emulsification of liquid fat in water yields only a hydrophobic system; but because water is soluble in soap (even such a solid

[1] J. PERRIN: Journal de Chimie Physique, **3**, 84 (1905).

[2] H. FREUNDLICH: Kolloid-Zeitschr, **3**, 80 (1908); Kapillarchemie, 309, Leipzig, (1909).

[3] WOLFGANG OSTWALD: Kolloid-Zeitschr., **1**, 291 and 331 (1907); Theoretical and Applied Colloid Chemistry, translated by MARTIN H. FISCHER, 40, New York (1917); Handbook of Colloid Chemistry, translated by MARTIN H. FISCHER, 2d Ed., 42, Phila. (1919).

[4] WOLFGANG OSTWALD: Kolloid-Zeitschr., **11**, 230 (1912).

soap as sodium stearate) a mixture of this with water yields a hydrophilic system. As the study of the lyophilic colloid systems from this point of view serves also to make clear certain of their other properties some illustrative facts taken from the colloid behavior of the soaps[1] may advantageously be introduced at this point. The discussion of the soaps from such a colloid-chemical point of view is particularly apt. First, they are typically lyophilic (hydrophilic) colloid systems and it is these which are of greatest biological importance (fibrin, gelatin, glue, starch, glycogen, dextrin, vegetable fibers, albumin, agar-agar, certain lipoids, etc., being all hydrophilic colloids); second, the soaps as salts of the fatty acids are the chemical analogs of the salts of the polymerized amino-(fatty)acids (the proteins) which constitute living matter.

§ 3

When a neutral soap like sodium oleate or sodium stearate is mixed with a limited volume of water (a 30 per cent "solution" of the former or a 10 per cent "solution" of the latter) and the mixture is brought to the temperature of a boiling water bath the whole yields a homogeneous solution. The water-like liquid shows all the properties characteristic of the "true" solutions like a normal osmotic pressure, electrical conductivity, etc. When now the temperature is allowed to fall (say to room temperature) the mixture becomes in both instances opalescent, increases enormously in viscosity and finally sets into a semi-solid or solid gel. With fall in temperature there has occurred, in other words, transformation to a typical lyophilic colloid system.

When now one tries to state in the simplest possible terms what it is that has happened when such a definite mixture of soap and water, which is a mobile liquid at the temperature of boiling water, is seen to set into a dry, solid mass as its temperature is reduced, it seems easiest to think of the whole as a change from what is, at the higher temperature, essentially a solution[2] of *soap*

[1] Martin H. Fischer and Marian O. Hooker: Science, **48**, 143 (1918); *ibid.*, **49**, 615 (1919); Chem. Engineer, **27**, 155, 184, 223, 253, 271 (1919).

[2] We are not unaware that the concept "solution" needs itself to be defined. While the field of "solution" constitutes slippery ground, we accept, for pragmatic reasons, as characteristic of the "true" solutions the teachings of Wolfgang Ostwald and P. P. von Weimarn who define such as dispersions of

in water to that which is, at the lower temperature, a solution of *water in soap*.[1] Between these extremes and as determined by the temperature and by the relative concentration of soap and of water we get various mixtures of solvated soap in soap-water or of soap-water in solvated soap. The situation in the case of the soaps in the presence of limited volumes of water is identical, in other words, with the changes which may be seen in mutually soluble systems of the type phenol/water, ether/water or protein/water as studied by J. FRIEDLÄNDER,[2] V. ROTHMUND,[3] W. B. HARDY,[4] WOLFGANG OSTWALD[5] and their various followers.

The behavior of the mutually soluble system phenol/water (which is considered particularly apt in the matter of understanding the colloid behavior of the system soap/water) is shown in Fig. 2. The bottle on the extreme left contains phenol only (which like any "pure" soap is a crystalline mass at the proper temperature). The succeeding bottles contain the same weight of phenol plus gradually increasing amounts of water. As more and more

A in B with the degree of subdivision measurable in molecular or smaller values. To express the matter in the terms of A. P. MATHEWS, we may say that A is dissolved in B or vice versa when the solvent has overcome the cohesive forces of the dissolved substances. As MATHEWS has shown, the forces of cohesion operate within molecular dimensions. To judge from our own impressions as gained by study of such systems as the chemist would call "concentrated solutions" we are of the opinion that "solution" means in most instances union of solvent with the dissolved material and vice versa. Such union is indisputable and attains enormous values in the case of the concentrated solutions. That it is ignored or has only small value assigned to it in the case of the standard "dilute" solutions is only because their general properties are dominated by the large excess of free "solvent" present.

[1] The distinction between these two types is not an academic one, as witness the differences in reaction of the two systems to such an indicator as phenolphthalein. A chemically neutral soap like sodium oleate, palmitate or stearate when dissolved in water will turn this indicator a bright red. When, however, the water is dissolved in the soap the indicator remains colorless. See page 775 or MARTIN H. FISCHER: Chem. Engineer, **27**, 271 (1919). Protoplasm is generally regarded as a solution of the protoplasmic substances in water; it is almost exactly the reverse, namely, protoplasmic substance which has dissolved a certain amount of water.

[2] J. FRIEDLÄNDER: Zeitschr. f. physik. Chemie, **38**, 430 (1901).

[3] V. ROTHMUND: Zeitschr. f. physik. Chem., **63**, 54 (1908).

[4] W. B. HARDY: Jour. Physiol., **24**, 158 (1899); Zeitschr. f. physik. Chem., **33**, 326 (1900).

[5] WOLFGANG OSTWALD: Kolloid-Zeitschr., **1**, 335 (1907); Theoretical and Applied Colloid Chemistry, translated by MARTIN H. FISCHER, 89, New York (1917).

water is added the phenol fails to crystallize; up to and including the sixth bottle from the left, only "solutions" are obtained but

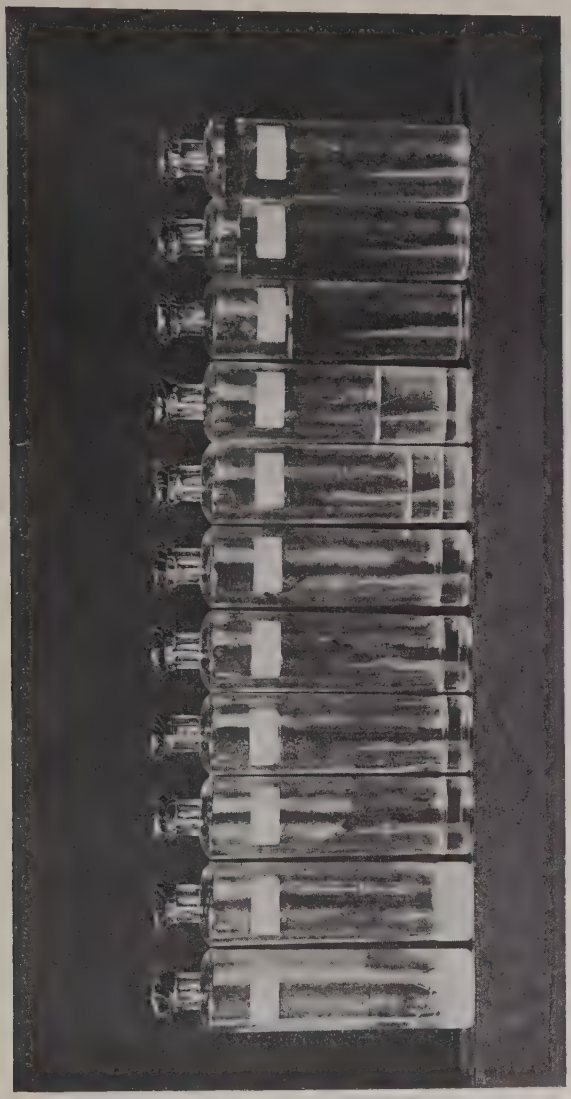


FIGURE 2.

these are solutions of *water in phenol.* The seventh bottle shows two layers; below, one of phenol saturated with water, above, a

solution of *phenol in water.* With further additions of water the later type of solution grows at the expense of the former until, finally, in the bottle second from the extreme right of the series nothing but a solution of phenol in water remains.[1]

Of importance for our further discussion is, first, the existence of *the two types of solution,* that of water in phenol and that of phenol in water. The physical constants of these two solutions are totally different and they behave differently, too, toward changes in external conditions like temperature or various added substances (acids, bases, salts, indicators, etc.). When a little methylene blue or malachite green, for example, is added to such a mixture as is represented in the seventh or eighth bottle of the series, the watered phenol phase stains deeply; while the phenolated water remains clear. A second point of importance is the behavior of such a system when subjected to increases or decreases in temperature. When the temperature is raised the watered-phenol phase goes over and into solution in the phenolated-water phase. It is characteristic of liquids, when their temperature is being lowered, to show a progressive increase in viscosity. The warmed solution of phenol-in-water also shows such a progressive increase in viscosity as its temperature is lowered, but, as first noted by Friedländer and Rothmund, this progressive increase shows a sharp break as soon as the critical temperature is reached, at which the phenol begins to separate out. This break expresses itself as a sharp *rise* in viscosity which increases for a time and then falls off again, so that with further lowering of temperature a viscosity curve more like the original "normal" is again obtained.

We are indebted to Wolfgang Ostwald for pointing out that, *in this critical zone during which the phenol/water system is opalescent and shows an abnormally high viscosity we are in reality dealing with a colloid system* (consisting of watered-phenol dispersed in phenolated-water).

Turning now to the study of the mechanism employed for the production of the soap colloid systems, it is evident that they are

[1] In analogy to what happens in the "salting out" of colloids it is well to explain the nature of the contents of the right-hand bottle in the series. This was originally nothing but a solution of phenol in water, but through the addition of ordinary table salt the phenol was "salted out" so that now a phenol phase with some water dissolved in it (analogous to a salted-out colloid of the biochemists or colloid chemists) is seen floating at the surface of the liquid in the bottle.

formed by " dissolving " a unit weight of soap in a definite volume of water at a rather high temperature. In the accepted parlance, it may be said that through such increase in temperature the solubility of the soap *in* the water is tremendously increased.

To illustrate in rather crude fashion the effects of a lowering of temperature, Fig. 3 (Diagrams A and B) is introduced. They show the results when any two mutually soluble substances, like water and soap, are mixed together. When the soap is readily soluble in the water and the concentration is rightly chosen there results a true solution at the higher temperature. This matter is represented by the region marked *A* in the diagrams (the soap is dispersed molecularly or ionically in the solvent). If, now, the temperature is lowered, the solubility of the soap in the water is decreased. As the saturation point for the lower temperature is attained, the soap particles assume not only molecular size but more than molecular size. By definition, therefore, we approach with falling temperature the realm of the colloids, or that of dispersions of one material in a second with the degree of dispersion showing dimensions greater than the molecular. The gradual increase in the size of the soap particles (or increase in their number) with lowering of the temperature is represented by the regions *B*, *C*, *D*, *E* and *F*.

Thus far has been explained merely the production of a colloid system by the ordinary process of bringing about supersaturation and an agglomeration of particles previously more highly dispersed. It is obvious that such agglomeration may yield either a so-called lyophobic or lyophilic colloid (or, depending upon the solid or liquid nature of the separating phase, a suspension or an emulsion colloid). *The lyophobic colloid results when the solvent is not soluble, the lyophilic when the solvent is soluble in the precipitating phase.* When soap falls out of solution from such a solvent as allyl alcohol the former of these possibilities is satisfied; when it falls out, as in our illustration, from water, the latter is satisfied. The black circles or crystal clusters in the diagrams of Fig. 3 represent more, therefore, in the latter instance than precipitates of pure soap; they are this, plus a certain amount of the water (or other " solvent ") dissolved in them.

At a sufficiently low temperature the soap aggregates will have become so large or so numerous as to touch and coalesce. If this process continues to a sufficient extent the system will

ultimately represent in essence nothing but soap in which the previous "solvent" is now dissolved. Diagrammatically this situation is represented by the zones *Z* of Fig. 3.

A glance at Fig. 3 shows, however, that between the upper extreme (*A*) of a solution of the soap in the solvent and the lower extreme (*Z*) of a solution of the solvent in the soap, there exist two main zones of mixed systems, — one below the upper (*B*, *C*, *D* and *E*) consisting of a dispersion of solvated-soap in the soaped-solvent, and a second above the lower (*Y*, *X*, *W*, and *V*) consisting of soaped-solvent in the solvated-soap. These two mixed

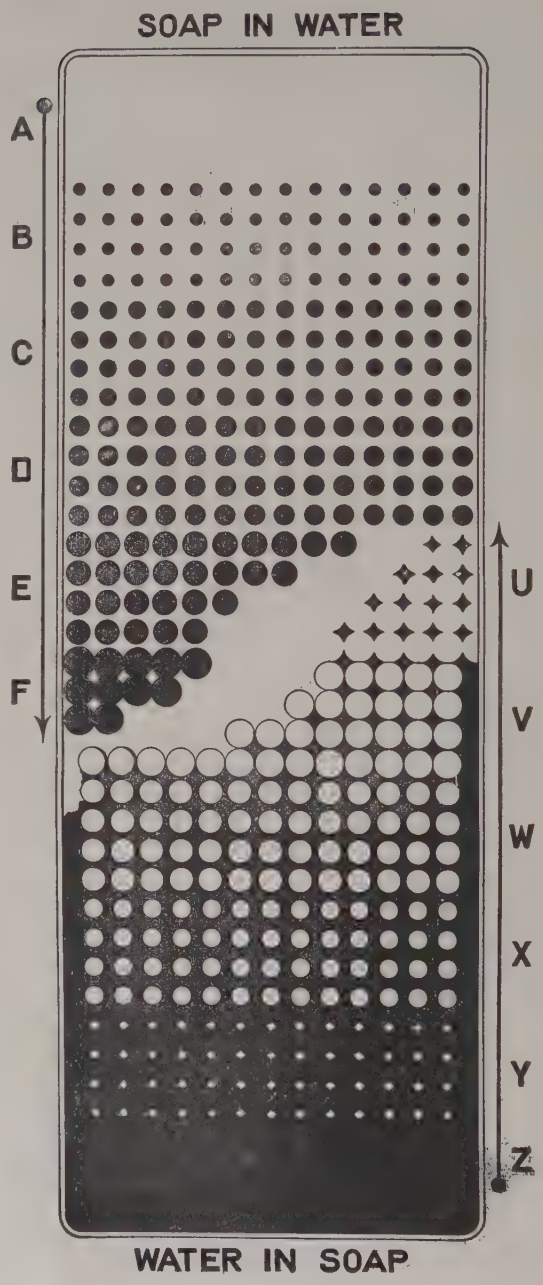


FIGURE 3 (Diagram A).

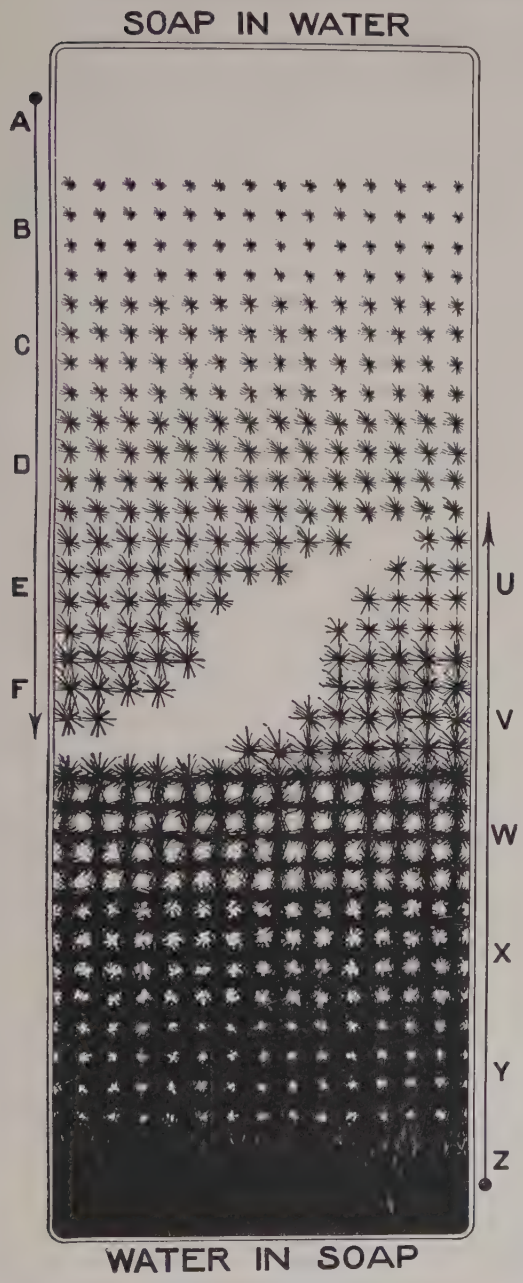


FIGURE 3 (Diagram B).

systems (if the soap is liquid) are in essence *emulsions, but of opposite type* and as such (even when of the same quantitative chemical constitution) are possessed of totally different physical properties. The former corresponds, for example, to an emulsion of oil-in-water, the second to one of water-in-oil, and as the former (as illustrated by milk) will mix with water, wet paper and show a certain viscosity value, the latter (as illustrated by butter) will mix only with oil, will grease paper and show an entirely different viscosity.[1]

Returning to the lyophilic soaps and the diagrams, it is obvious that

[1] See in this connection MARTIN H. FISCHER and MARIAN O. HOOKER: Science, **43**, 468 (1916); Fats and Fatty Degeneration, 20, New York (1917).

as we descend with lowering of temperature from the region *A*, we pass in the regions *B*, *C* and *D* through increasingly viscid liquid colloid "solutions" (so-called *sols*) but all of them emulsions of the type solvated-soap in soap-water. In the region *E*, the particles of solvated soap almost touch and here the highest (liquid) viscosity is obtained. In *F* they do touch and now form a continuous *external* phase. At this point we change to the opposite type of emulsion (to one of soap-water in solvated-soap) and the previously liquid colloid becomes solid. As ordinarily put, the mixture *gels*.

It is of interest next to emphasize how this concept of the changes which a soap/water system suffers in passing from a liquid sol to a dry gel may help to explain various of the "strange" characteristics of colloid systems.

A first question under this heading is that of the nature of *hysteresis*, more particularly that observed when a colloid is subjected to changes in temperature. The importance of the thermal history of a colloid system is constantly stressed. It is generally true of the lyophilic colloids that, when subjected to heat manipulation, they tend to hold fast to the characteristics of their previous states. A colloid on cooling, for example, first sets at a certain temperature; yet the same colloid after setting, on reheating fails to liquefy at this temperature—it usually first "melts" at a higher one. In fact, it may be said quite generally that the curve showing the increase in viscosity of a lyophilic colloid with *lowering* of temperature is rarely identical with that portraying the decrease in viscosity when the temperature is *raised* through the same range. If the fact is remembered that the absolute *values* of two mutually soluble substances are rarely the same and that the *rates* at which they go into solution in each other are usually different, many of these difficulties disappear. Fig. 3 shows diagrammatically, not only what happens when the temperature of a solution of soap in water is lowered, but in the lower half of the pictures the effects of warming a gel. Increasing the temperature of the original solvated-soap shown in region *Z* increases the solubility of the soap in the water, and so the colloid dispersion *Y* results, consisting of soap-water in solvated-soap. Further increase in temperature yields the regions *X* and *W*, but, because of the persistence of the solvated-soap as the *external* phase, all these regions continue to show a rigidity or viscosity

higher than that of systems of the same quantitative composition produced by a lowering of temperature from a higher level. The gel first shows signs of liquefaction when the soap-water particles begin to touch and thus form the external phase, as in the regions *V* and *U*. It is for these reasons that *the region of greatest ambiguity and of greatest hysteresis is found in the broken middle portions of the diagrams* (*D, E, F, and W, V, U*). Just as long periods of time are required to make solution phenomena attain their end values, just so must mutually soluble systems subjected to changes in their environment be expected to come only slowly into a state of final equilibrium.

In addition to this closer definition of hysteresis it is possible also to define more accurately *gelation capacity* and *solvation or hydration capacity* of a colloid. The latter measures the solubility of the solvent in the colloid material and is synonymous with *swelling* capacity. Gelation, however, includes not only this value but more—namely, everything embraced within the region of the emulsification of a "solution" of the colloid material in the solvent within the solvated colloid as an external "dry" phase. It embraces everything in Fig. 3 up to and including the zone *V*.

Just above this region it is apparent that the more solid phase may no longer be adequate to enclose all the "solution" of colloid in solvent. When this upper region is reached the colloid system tends to "sweat"—or to use the term of Thomas Graham the gel shows *syneresis*. We may still have before us a gel, but it is now no longer "dry."

To go sufficiently above the region *U* is to be in the regions *E* and *D*. We now no longer say that there is syneresis or that this has become excessive, but we say that the gel has gone into or persists in the *sol* state.

It is of importance now to point out that in the discussion of Fig. 3 we have referred oftenest to Diagram A, in which it is assumed that the material (like soap) which falls out with a lowering of temperature is *liquid* in character. This, of course, it need not be. It may be solid. The matter is of importance in determining the physical properties of the systems which are ultimately obtained. When sodium oleate, for example, falls out in water at ordinary temperatures, it does so in liquid form, but when sodium stearate is the soap in the system, it comes out in crystal-

line form, yielding a system like Diagram B). From both are derived hydrated or solvated systems, but it is obvious that crystals cannot be packed as uniformly or as compactly as can droplets. If the ultimate system consists of a solid mixed with liquid, it will approximate in physical characteristics such a mixture as that of sand with water, but, if it consists of a liquid mixed with liquid, its properties will more nearly approximate an emulsion, as when a liquid oil is mixed with a liquid protein to form a mayonnaise. Systems of the former type will, for example, be more brittle, show more sudden transitions in physical properties, permit of a more rapid separation of the one phase from the other and will sweat more easily and over longer ranges (show syneresis) than will the second group.[1]

As a final word it needs to be emphasized that *the concept of the lyophilic colloid as here outlined sets no limitations upon the nature of the materials that may make up such a system and makes no specification as to the nature of the forces which guarantee the stability of the colloid system.* They are, in general, any or all the forces which appear in or are operative in solutions of the most varied kinds. This is emphasized because there has been much written, for example, regarding the all-important effects of such single elements as the electrical charges in determining the stability of colloids in general and of the lyophilic colloids in particular. We do not wish to deny the importance of this factor in *some* colloid systems or under *certain* conditions, but it is too narrow a view to take of what constitutes the lyophilic colloids in general. While the play of electrical forces may be apparent in systems composed of soaps and water or proteins and water, lyophilic colloid systems may be built up in which the electric factors are either negligible or absent. It is somewhat difficult, to say the least, to conjure up orthodox electrical notions in such beautiful gels as may be made from nothing but soaps with anhydrous alcohol, toluene, benzene, chloroform or ether.

[1] It is in this larger classification of the colloid systems (after their definition as lyophobic or lyophilic systems in the terms given above) that the concepts of Wolfgang Ostwald covering the importance of the physical state (gaseous, liquid and solid) of the phases subdivided into each are of such fundamental significance.

With these remarks in mind on the nature of the lyophilic or hydrophilic colloids in general we may now turn to a more specific study of such as appear in living cells. When it is recalled that the hydrophilic colloids which have thus far been accorded most study—gelatin, glue, albumin, dextrin, starch, vegetable fibers, gums—are all derived from biological sources, their probable importance in the living animal or plant must at once be suspected. Not only is the chief mass of the living organism built up of colloid material, but most of it belongs in the hydrophilic group. We will not be surprised, in consequence, to find that those physico-chemical characteristics which made for the division of all colloids into two great classes will show themselves of importance in determining the behavior of the tissues toward water.

It will give us a better conception of just what this absorption of water by colloids represents, and how it is influenced through various external conditions, if we study the swelling of some proteins.

2. Observations on the Swelling of Fibrin

In these experiments ordinary blood fibrin was used, which after having been thoroughly washed to free it from adhering salts was dried at a low temperature and pulverized in a mortar. When weighed amounts of such powdered fibrin (0.25 gram) are introduced into definite volumes (25 cc.) of various solutions contained in test-tubes of the same diameter (1.7 cm.) the fibrin swells to very different heights. From the results of many series of experiments, the following facts which are of importance in our discussion have been determined.[1]

(*a*) Fibrin swells more in the solution of any acid than it does in distilled water. Table I illustrates this fact. While the exact order changes somewhat at different concentrations the table also serves to indicate that when equinormal acids are compared, they are found to be very unequally effective in producing the swelling. A hasty glance suffices to show that we are not dealing with the simple effects of hydrogen

[1] See Martin H. Fischer and Gertrude Moore: Am. Jour. Physiology, **20**, 313 (1907); Kolloid-Zeitschr., **5**, 197 (1909); Martin H. Fischer, Pflüger's Archiv., **125**, 99 (1908).

ions determined by the relative degrees of dissociation of the various acids, for while a "strong" acid (hydrochloric) stands at the top of the list, another (sulphuric) stands at the very bottom, while a series of "weak" organic acids are found between.

TABLE I

FIBRIN—*Acid*

All acids n/10	Height of fibrin column in mm. after 24 hours.	All acids n/10	Height of fibrin column in mm. after 24 hours.
Water	6	Oxalic	24
Hydrochloric	28	Nitric	20
Phosphoric	27	Acetic	10
Lactic	27	Citric	9
Formic	24	Sulphuric	8

The amount that fibrin swells in any acid solution is dependent upon the concentration of the acid. Within certain limits fibrin swells the more the higher the concentration of the acid. In the case of the "strong" acids, however, a maximum is attained, above which a further increase in the concentration of the acid does not lead to a greater, but to a diminished absorption of water. The swelling of fibrin in acid solutions of progressively higher concentrations may therefore be represented graphically by a curve which rises at first, attains a maximum and then falls again. These facts are brought out in Table II. In the case of acetic acid it will be noted that the highest concentration of acid used in the table induces the greatest amount of swelling. At concentrations above n/10, I obtained a height up to 41 mm. with this acid. As yet I have not, however, been able to determine if with such a "weak" acid a point is finally reached beyond which, as with the "strong" acids, a further increase in concentration brings about a diminished absorption. No greater swelling of fibrin than that noted in the table can be obtained by using concentrations of sulphuric acid above those given in Table II.

(*b*) Fibrin swells more in the solution of any alkali than in pure water, but the amount of this swelling is greater in

TABLE II

FIBRIN—*Acid*

Concentration of acid.	Height of fibrin column in mm. after 24 hours in			
	Hydrochloric acid.	Nitric acid.	Acetic acid.	Sulphuric acid.
1 cc. n/10 acid +24 cc. H_2O	12	13.5	8.5	8.
2 " " +23 "	23	26.	10.	9.
3 " " +22 "	37	29.	10.5	9.5
4 " " +21 "	47	**37.5**	11.	10.
5 " " +20 "	**48**	35.	12.	10.
6 " " +19 "	.....	30.	12.	**11.**
7 " " +18 "	.....	30.	13.	11.
8 " " +17 "	.....	25.	13.	10.
9 " " +16 "	.....	23.	14.	10.
10 " " +15 "	41	21.5	14.5	10.
12½ " " +12½ "	.....	18.5	15.	10.
15 " " +10 "	31	17.	16.	9.
17½ " " + 7½ "	.....	14.5	17.	9.
20 " " + 5 "	.....	14.	18.	8.5
25 " "	21	11.5	**18.5**	8.5
25 " water (control)	8	8.	8.	8.

some alkalies than in others. This statement is the analog of the corresponding one for acids. When equinormal solutions are compared fibrin swells more in potassium hydroxid than in sodium hydroxid, and more in either of these than in calcium hydroxid or ammonium hydroxid in the order named.

The first three of these have in such dilute solutions about the same degree of dissociation. Clearly, the amount of swelling is not simply a function of the hydroxyl ions. As in the case of acids, the amount of swelling is here also dependent upon the concentration of the alkali. For the "strong" alkalies there is within certain limits an increase in the amount of swelling with every increase in the concentration of the alkali, but, after a certain point is exceeded a further increase in concentration is followed by a diminution in the height of the fibrin column. Tables III and IV illustrate these facts.

If the amounts that fibrin will swell in acid and alkali solutions having the same H or OH concentration are compared, it is found that fibrin swells less in the solution of an acid than in an equally concentrated solution of an alkali. While, for

example, in n/50 KOH or NaOH, the fibrin column may be found to measure 83 and 77 mm. respectively, in n/50 HCl or HNO_3 it measures only 48 and 35 mm.

TABLE III

FIBRIN—*Alkali*

Concentration of alkali.	Height of fibrin column in mm. after 24 hours.		
	KOH	NaOH	NH_4OH
2 cc. n/10 alkali +23 cc. H_2O	23	22	10
4 " " +21 "	64	58	10.5
6 " " +19 "	**83**	**77**	11
10 " " +15 "	80	75	11
15 " " +10 "	72	62	12
25 " "	58	57	**13**
25 cc. water (control)	8	8	8

TABLE IV

FIBRIN—*Alkali*

Concentration of alkali.	Height of fibrin column in mm. after 24 hours.	
	NaOH	$Ca(OH)_2$[1]
1 cc. n/10 alkali +24 cc. H_2O	12.5	13
2 " " +23 "	23	15
3 " " +22 "	40	17
4 " " +21 "	66	18
5 " " +20 "	75	**18**
6 " " +19 "	**75**	15
7 " " +18 "	75	16
8 " " +17 "	74	15
9 " " +16 "	73	
10 " " +15 "	68	
12½ " " +12½ "	64	
15 " " +10 "	61	
17½ " " + 7½ "	57	
20 " " + 5 "	57	
25 " "	53	
25 cc. water (control)	8	

[1] Actually these solutions were prepared by diluting n/30 $Ca(OH)_2$.

(*c*) We come now to the interesting fact that the addition of any salt to the solution of an acid or an alkali decreases the amount that fibrin will swell in that solution. The only exceptions to this rule are formed by the salts which react with the acids. If barium chlorid, for example, is added to a sulphuric acid solution, the amount of swelling is not decreased, but in-

creased. This is because insoluble barium sulphate is produced and thrown down, while hydrochloric acid is formed in which fibrin swells more than in an equally concentrated sulphuric acid solution.

The higher the concentration of the added salt, the less does the fibrin swell, and if enough is added the effect of the acid or alkali may be suppressed almost entirely. These facts are illustrated in Tables V and VI and in Fig. 4. The tube on the

FIGURE 4.

extreme right contains the unit weight of powdered fibrin in water. The tube marked HCl contains the same weight of fibrin in n/40 acid. The remaining tubes from right to left contain the same amounts of acid and of fibrin, but progressively greater concentrations of sodium nitrate (from m/40 to m/5 in the finished solution).

(*d*) If the effect of equimolar [1] salt solutions is compared,

[1] To make proper comparisons between the physiological or pharmacological actions of different chemical compounds, ordinary equivalents by weight (as in percentage solutions) cannot be used. We must compare

TABLE V

FIBRIN—*Acid+Salt*

Concentration of solution.	Height of fibrin column in mm. after 24 hours.			
	KCl	$MgCl_2$	$(NH_4)_2SO_4$	KI
15 cc. n/5 HCl +15 cc. m/2 salt solution	9	6	5	5
15 " " +15 " m/4 "	10	8	6	5
15 " " +15 " m/8 "	13	9	7	6
15 " " +15 " m/16 "	14	10	10 (?)	10 (?)
15 " " +15 " m/32 "	15	10	9	9
15 " " +15 cc. water (control) 17				

TABLE VI

FIBRIN—*Alkali+Salt*

Concentration of solution.	Height of fibrin column in mm. after 24 hours.
5 cc. n/10 NaOH +12 cc. m/1 NaCl + 8 cc. H_2O	19
5 " " +10 " " +10 "	21
5 " " + 8 " " +12 "	21
5 " " + 6 " " +14 "	24
5 " " + 4 " " +16 "	28
5 " " + 3 " " +17 "	30
5 " " + 2 " " +18 "	32
5 " " + 1 " " +19 "	43
5 " " +20 cc. water	74
25 cc. water (control)	8

amounts that are equivalent from certain chemical or physico-chemical points of view. For many purposes *molar* (*gram-molecular* or *molecular*) *solutions* serve very well. A molar solution (m/1) is made by dissolving the molecular weight of the substance (including its water of crystallization, if it has any) expressed in grams in enough water to make a liter. If only one-half the gram-molecular weight is dissolved in enough water to make a liter, we have a one-half molar solution (m/2), etc. Solutions which contain the same number or fractions of a gram-molecule in the unit volume are equimolar.

In the case of acids and alkalies it is usually best to employ *normal* solutions. A normal solution (n/1) is a molar one provided the dissolved substance is monobasic. In other words, its power to displace hydrogen is taken into consideration. A normal solution of a dibasic compound has half the concentration of a molar solution of the same compound; a normal solution of a tribasic compound but one-third, etc. Equinormal solutions of different acids or alkalies therefore all contain the same amount of replaceable hydrogen or hydroxyl.

The "physiological" or "normal" salt solutions of our laboratories and hospitals have absolutely nothing to do with the normal solutions of the chemists which we are discussing. The terms are meaningless, and should disappear. We should speak of 0.85 per cent or 0.9 per cent sodium chlorid solutions if that is what we mean by these terms.

they are found to affect the swelling of fibrin in solutions of acids or alkalies to very unequal degree. This is readily apparent from Fig. 5. where the effect of adding molecularly equivalent amounts of various sodium salts to a hydrochloric acid solution is portrayed. The tube on the extreme left contains pure water only. The next contains pure hydrochloric acid (n/40). From left to right the succeeding tubes contain the same amount of hydrochloric acid plus various sodium salts (n/40 HCl in m/40

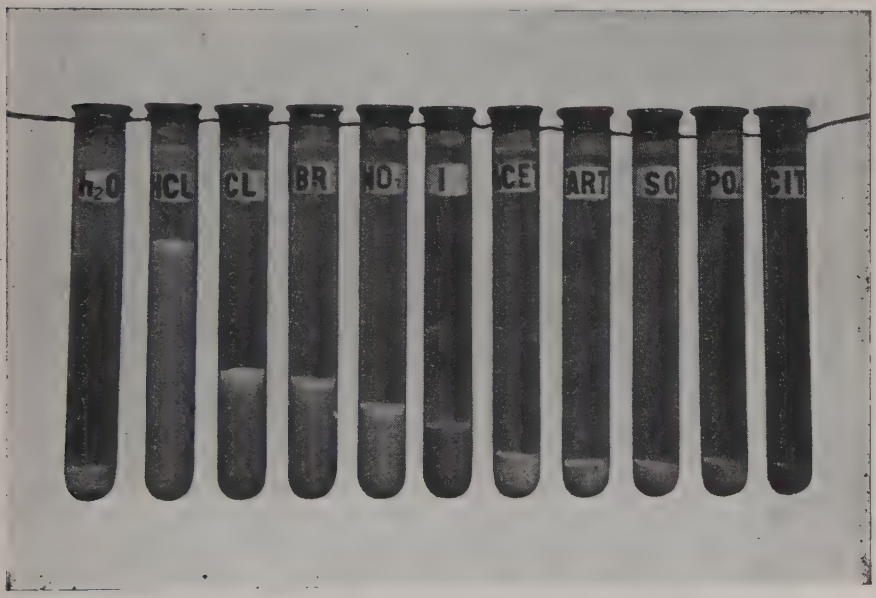


FIGURE 5.

salt solution). The salts added from left to right are respectively the chlorid, bromid, nitrate, iodid, acetate, tartrate (of sodium and potassium), sulphate, phosphate and citrate of sodium.

The tube on the extreme left in Fig. 6 contains a pure n/40 solution of sodium hydroxid. The remaining tubes show the effect of adding molecularly equivalent (m/40) amounts of various sodium salts to the pure sodium hydroxid solution. From left to right the salts added are the bromid, nitrate, acetate, tartrate, sulphate, citrate and phosphate of sodium.

FIGURE 6.

From the study of many series of salts it has been found that the effect of any salt is made up of the sum of the effects of its constituent radicals. In any series of salts having a common base the order in which the acid radicals are effective is always found to be the same, and when series having a common acid are compared, the order in which the basic radicals are effective is always the same. From such experiments the two following lists have been constructed. The radical least effective in bringing about a diminution in the amount that fibrin will swell in the solution of any acid or alkali is in each case placed first:

Acid radicals.	*Basic radicals.*
Chlorid	Potassium
Bromid	Sodium
Nitrate	Ammonium (?)
Sulphocyanate	Magnesium
Iodid	Calcium
Acetate	Barium
Sulphate	Strontium
Phosphate	Copper (ic)
Tartrate	
Citrate	Iron (ic)

The table for the acid radicals is more accurate than the table for the basic radicals. This is because the amount of difference in swelling produced by the end members of each of the two series is decidedly greater in the case of the acid radicals than in the case of the basic radicals. The general grouping of the basic radicals is, however, entirely trustworthy. While the difference between the amount of swelling in an acid solution containing a magnesium salt may not differ decidedly from a similar solution made up with a calcium or barium salt, there is never any question about the difference between the action of any of these three and that of a radical found in the list either above or below them.

(*e*) Non-electrolytes do not share with electrolytes their marked power of reducing through their presence the amount that fibrin will swell in the solution of any alkali or acid. In concentrations that are from an osmotic standpoint comparable to those used above in the case of salts, the non-electrolytes are almost without effect, as shown in Tables VII and VIII:

TABLE VII

FIBRIN—*Acid+Non-electrolytes*

Concentration of the solution.	Height of fibrin column in mm. after 24 hours.
10 cc. n/5 HCl+10 cc. H_2O	28
10 " " +10 " m/1 glycerin	30
10 " " +10 " " saccharose	28
10 " " +10 " " urea	27.5
10 " " +10 " " dextrose	27
20 cc. water (control)	8

TABLE VIII

FIBRIN—*Alkali+Non-electrolytes*

Concentration of the solution.	Height of fibrin column in mm. after 24 hours
10 cc. n/10 KOH + 4 cc. m/1 ethyl alcohol +11 cc. H_2O	76
10 " " +4 " " methyl alcohol +11 "	77
10 " " + 4 " " glycerin +11 "	72
10 " " + 4 " " urea +11 "	83
10 " " + 4 " " saccharose +11 "	75
10 " " +15 " H_2O	77
10 " " +10 " 2/m ethyl alcohol + 5 "	73
10 " " +10 " " methyl alcohol + 5 "	73
10 " " +10 " " glycerin + 5 "	64
10 " " +10 " " urea + 5 "	80
10 " " +15 " m/1 saccharose	75
10 " " +15 " H_2O	78
25 cc. water (control)	8

Not until employed in rather concentrated solutions do glycerin, saccharose, dextrose, ethyl alcohol and methyl alcohol change in any marked way the height to which a fibrin column will swell in various concentrations of acid or alkali.

(*f*) For purposes of biological application a series of tables are inserted here which show the effect of different non-electrolytes upon the absorption of water in a *neutral* medium. Saccharose, dextrose, levulose, methyl alcohol, propyl alcohol and acetone will inhibit more or less markedly the amount of water that fibrin will absorb.[1] Of these, the behavior of saccharose, dextrose and levulose deserve special mention. While all three dehydrate fibrin in increasing amount with increase in concentration, at the same concentration saccharose is the most powerful in

[1] MARTIN H. FISCHER and ANNE SYKES: Kolloid-Zeitschr., **14**, 215 (1914).

this regard. Tables IX, X and XI suffice to illustrate this fact, which will be more emphatically brought out in discussing the absorption of water by gelatin.

TABLE IX

FIBRIN—*Saccharose*

Concentration of solution.	Height of fibrin column in mm.
40 cc. water (control)	23
1 cc. 2/m saccharose +39 cc. H_2O	22
2 " " +38 "	22
3 " " +37 "	21
5 " " +35 "	21
7½ " " +32½ "	21
10 " " +30 "	20
20 " " +20 "	18

TABLE X

FIBRIN—*Dextrose*

Concentration of solution.	Height of fibrin column in mm.
40 cc. water (control)	21
1 cc. 2/m dextrose +39 cc. H_2O	21
2 " " +38 "	20
3 " " +37 "	20
5 " " +35 "	19
7½ " " +32½ "	19
10 " " +30 "	18
20 " " +20 "	17
40 " "	15

TABLE XI

FIBRIN—*Levulose*

Concentration of solution.	Height of fibrin column in mm.
40 cc. water	21
1 cc. 2/m levulose +39 cc. H_2O	20.5
2 " " +38 "	20.5
3 " " +37 "	20.5
5 " " +35 "	20
7½ " " +32½ "	20
10 " " +30 "	20
20 " " +20 "	19

(*g*) The taking up and giving off (absorption and secretion) of water by fibrin represents in high degree a reversible process.

If for a hydrochloric acid solution in which fibrin has attained its maximal swelling, an equally concentrated sulphuric acid solution is substituted, the fibrin column shrinks. The same occurs if a potassium hydroxid solution is replaced by an equally concentrated calcium or ammonium hydroxid solution. When equilibrium is finally established the height of the fibrin column in each of these solutions is approximately equal to that which would have been attained had the fibrin been placed directly in these solutions. In the same way fibrin which has attained its maximal swelling in an acid solution will shrink rapidly if for the pure acid there is substituted one of equal concentration containing a salt. Similarly, if water replaces the solution of an acid or an alkali, the fibrin will either shrink or swell more, depending upon whether the addition of the water makes the concentration of the alkali move toward or away from that which is optimal for the swelling of fibrin. (See paragraph *b* of this section.)

The reverse of all these experiments can also be accomplished, although not with the same ease. If, for example, hydrochloric acid is substituted for sulphuric, or potassium hydroxid for the calcium compound, an increase in the amount of swelling is noted, but the column does not rise as high as it would have done if placed directly in these solutions. Similarly, fibrin which has once been in an acid or an alkali solution containing a salt, when placed in pure solutions of acid or alkali does not swell to the amount which it would have done if it had been put in these solutions from the first. All this would seem to indicate that fibrin suffers more or less permanently from every external condition to which it has been subjected. To explain this phenomenon, which is of great importance from both the theoretical and the practical aspects of biology and medicine, we can advantageously call to mind the well-known property of colloids of attaching to themselves, and holding fast the various substances with which they come in contact.[1]

(*h*) For reasons associated with our analysis of the problem of œdema we are particularly interested in substances which are capable of increasing the amount of water held by such a colloid as fibrin. Among other substances besides acids and alkalies

[1] See page 210, where is discussed the taking up of dissolved substances and the phenomena of *adsorption*.

capable of thus increasing the hydration capacity may be mentioned urea and pyridin.[1] The hydrating effect of urea is already indicated in Tables VII and VIII, but is more clearly evidenced in Table XII. The hydrating effect of pyridin is illustrated in Table XIII. The calibrated test-tubes used in these particular experiments were 22 mm. in diameter, 40 cc. of solution were prepared and a gram of dry fibrin was employed.

TABLE XII

FIBRIN—*Urea*

Concentration of solution.	Height of fibrin column in mm. after 24 hours.
40 cc. water (control)	17
1 cc. 5/m urea +39 cc. H_2O	18
2 " " +38 "	19
3 " " +37 "	19
5 " " +35 "	19
7½ " " +32½ "	20
10 " " +30 "	22
20 " " +20 "	25
40 " "	39

TABLE XIII

FIBRIN—*Pyridin*

Concentration of solution.	Height of fibrin column in mm. after 24 hours.
40 cc. water (control)	20
1 cc. 10/m pyridin +39 cc. H_2O	22
2 " " +38 "	23
3 " " +37 "	24
5 " " +35 "	25
7½ " " +32½ "	26
10 " "	28

(*i*) An interesting and biologically important difference exists between the increased hydration brought about by substances of the type of urea or pyridin and that brought about through acids. That produced through acids is readily reducible through all salts. Salts do not reduce the increased hydration brought about either through urea or pyridin, as shown by Tables XIV

[1] See MARTIN H. FISCHER and ANNE SYKES: Science, **38**, 486 (1913). Some of the amins seem also to belong in this group, but they are so pronouncedly alkaline in watery solution that a large part of their hydrating effect seems to be dependent upon this alone.

and XV. The slight power of some salts to increase the hydration of (neutral) fibrin is merely found added to that produced by urea or pyridin alone. On the other hand, various non-electrolytes, such as the sugars, which affect the swelling of fibrin in acid solutions but little, produce a marked shrinkage when the increased hydration has been produced by urea or pyridin. This is shown in Tables XVI and XVII.

TABLE XIV

FIBRIN—*Urea*+NaCl

Concentration of solution.	Height of fibrin column in mm. after 24 hours.
40 cc. water (control)	18
20 cc. 5/m urea +20 cc. H_2O	30
20 " " +20 cc. m/1 NaCl	36
20 " " +15 " " + 5 cc. H_2O	35
20 " " +10 " " +10 "	35
20 " " + 5 " " +15 "	33
20 " " + 2½ " " +17½ "	33
20 " " + 1 " " +19 "	32

TABLE XV

FIBRIN—*Pyridin*+NaCl

Concentration of solution.	Height of fibrin column in mm. after 24 hours.
40 cc. water (control)	20
10 cc. 10/m pyridin +30 cc. H_2O	29
10 " " +20 cc. m/1 NaCl +10 cc. H_2O	32
10 " " +10 " " +20 "	32
10 " " + 5 " " +25 "	31
10 " " + 2½ " " +27½ "	30

TABLE XVI

FIBRIN—*Urea*+*Saccharose*

Concentration of solution.	Height of fibrin column in mm. after 24 hours.
40 cc. water (control)	19
20 cc. 5/m urea +20 cc. H_2O	29
20 " " +20 cc. 2/m saccharose	20
20 " " +15 " " + 5 cc. H_2O	20
20 " " +10 " " +10 "	20
20 " " + 5 " " +15 "	20
20 " " + 3 " " +17 "	20
20 " " + 2 " " +18 "	20
20 " " + 1 " " +19 "	21

TABLE XVII

FIBRIN—*Pyridin+Saccharose*

Concentration of solution.	Height of fibrin column in mm. after 24 hours.
40 cc. water (control)	20
10 cc. 10/m pyridin +30 cc. H_2O	29
10 " " +20 cc. 2/m saccharose +10 cc. H_2O	25
10 " " +10 " " +20 "	26
10 " " + 5 " " +25 "	27
10 " " + 2½ " " +27½ "	28

3. Observations on the Swelling of Gelatin

We have now to consider whether the behavior of fibrin in various solutions is characteristic of this substance alone, or whether we have simply discussed as applicable to *one* colloid, properties that are really common to many. A partial answer to this question can be found in the careful studies available on the swelling of gelatin and other proteins. The observations of FRANZ HOFMEISTER,[1] WOLFGANG PAULI,[2] K. SPIRO[3] and WOLFGANG OSTWALD[4] show gelatin to behave in many ways similarly to fibrin. We will review some of these in so far as they are of interest to us in the study of our problem. At the same time experiments of our own will be introduced which not only serve to corroborate the various findings already made on the swelling of gelatin but augment these, particularly in the following directions. They show (1) the unequal effect of different equinormal and equally dissociated acids and alkalies upon the swelling; (2) the antagonism between neutral salts and acids or alkalies upon it; (3) the comparative lack of antagonism between non-electrolytes and acids or alkalies upon the absorption of water by this substance; (4) the reversibility of the absorption of water by this substance. They discuss also (5) other substances besides acids which are capable of increasing the hydration capacity of gelatin and show (6) how such hydration is not reduced through salts, but readily through various non-electrolytes which are

[1] FRANZ HOFMEISTER: Archiv. f. exp. Path. u. Pharm., **27**, 395 (1890).
[2] WOLFGANG PAULI: Pflüger's Archiv., **67**, 219 (1897); ibid., **71**, 1 (1898).
[3] K. SPIRO: Hofmeister's Beiträge zur chem. Physiologie, **5**, 276 (1904).
[4] WOLFGANG OSTWALD: Pflüger's Arch., **108**, 563 (1905).

comparatively ineffective in reducing the swelling induced through acid.

Our experimental methods differed in no material way from those usually followed by workers in this field. OSTWALD'S scheme was adopted. One part of the best commercial gelatin was dissolved at a low temperature (45° C.) in four parts of water and poured into shallow pans. After having hardened in an ice-chest the gelatin was cut with the aid of a sharp knife and a ruler into squares of uniform size. These squares were allowed to dry upon glass plates at room temperature. The drying process took from six to ten days, and was not sufficiently rapid to distort the squares. When completely dry the squares measured about $18 \times 18 \times 2.5$ mm. and weighed approximately 0.8 gram. As a uniform material is necessary to obtain comparable results, it is well to mention that all the gelatin discs used in any extended series of experiments were always prepared at the same time. The course of the absorption of water by the discs was followed by immersing the weighed gelatin discs in solutions of various kinds and weighing them at intervals.

In order to facilitate comparison with the results obtained on fibrin the paragraphs on gelatin are lettered in the same way as the paragraphs on fibrin. It will be seen that gelatin is a colloid which behaves in many ways like fibrin. Important differences, however, exist between the two, which we shall later find to be not without biological interest.

(*a*) Gelatin swells more in the solution of any acid than it does in water. This fact is readily apparent even to the naked eye. If two gelatin discs are dropped at the same time, the one into water, the other into n/20 hydrochloric acid, the inequality in the amount of swelling is plainly to be seen at the end of six hours, and at the end of twenty-four or forty-eight it is very marked. While at this time the gelatin disc in the water still has a slightly brownish-yellow and opaque appearance, that in the acid is hyalin and perfectly clear, so clear, in fact, that it can scarcely be seen at the bottom of the dish. SPIRO, who first discovered this difference in the amount that gelatin will swell in water and in acids, found that while a gelatin plate gained 1.97 times its weight in water, it gained 3.49 times its weight in n/500 hydrochloric acid, and 5.45 times its weight in n/200 acid. OSTWALD came to the same conclusion from comparison

of his results on the swelling of gelatin plates in acids of various kinds with the absorption curves of gelatin in water, as given by HOFMEISTER.

While the gelatin swells more in the solution of any acid than in water, the acids are by no means equally potent in this regard when equinormal solutions are compared. Most authors are inclined to the belief that the swelling induced in gelatin discs is exclusively a function of the hydrogen ion concentration. It seems to me that this is only in part responsible for the observed effects. I have taken the liberty of constructing from OSTWALD'S [1] tables the curves contained in Figs. 7 and 8.

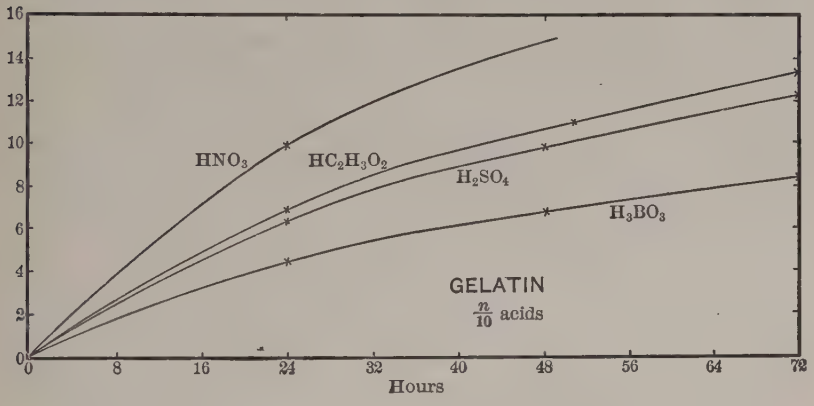


FIGURE 7.

The hours that the gelatin discs were in the acid solutions are plotted on the horizontal, the amount of water absorbed, expressed in units of the original weight of the disc, is shown on the vertical. We have no difficulty in recognizing in Fig. 7 the order:

Nitric, Acetic, Sulphuric, Boric.

The position of the " weak " acetic acid between the " strong " nitric and sulphuric acids (which two are about equally dissociated, and yield a higher concentration of hydrogen ions than the equinormal acetic acid) is by itself an argument against the explanation which considers *only* the concentration of the hydrogen

[1] WOLFGANG OSTWALD: Pflüger's Arch., **108**, 577 and 578 (1905).

ions. A look at Fig. 8 brings with it similar conclusions. Except in the first hours of the experiment, we again find the order:

Hydrochloric, Nitric, Acetic, Sulphuric, Boric.

This order in which the different acids make gelatin swell is identical with that in which they make fibrin swell.

The amount that gelatin swells in any acid solution is dependent in a complex way upon the concentration of the acid. This is shown in Fig. **9**, which has been copied from OSTWALD'S

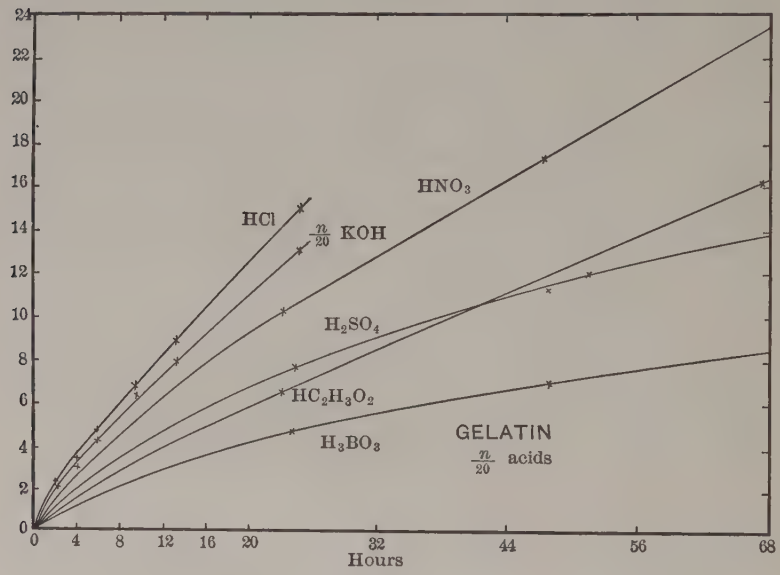


FIGURE 8.

article. The curve marked HCl indicates the amount of water absorbed by gelatin plates after twenty-four hours residence in hydrochloric acid solutions of various concentrations. With the exception of the initial fall in the curve (which simply indicates that in hydrochloric acid solutions of certain concentrations a gelatin disc may absorb even *less* than in pure water) we notice a rapid rise in the curve indicative of an increase in the amount of swelling with every increase in the concentration of the acid. An optimal point is reached when the concentration of (approximately) n/38 hydrochloric acid is attained, beyond which a

further increase in the concentration of the acid is not followed by a greater absorption of water, but by a less.

An analogous relationship between concentration of acid and amount of swelling exists in the case of fibrin.

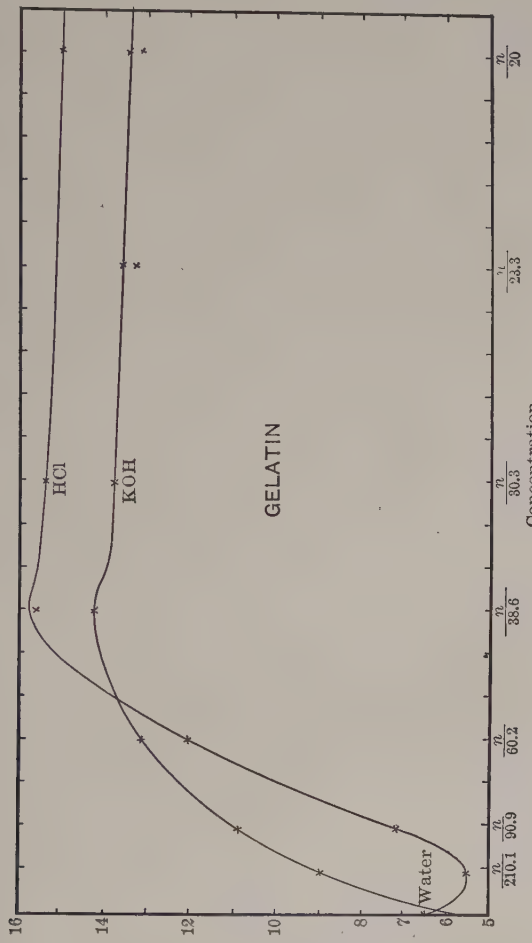


FIGURE 9.

(*b*) Gelatin swells more in the solution of any alkali than in water. Macroscopic examination alone evidences this fact. SPIRO,[1] who first noted it, found that while a gelatin disc kept in pure water gained only 3.02 times its weight of water, one kept

[1] K. SPIRO: Hofmeister's Beiträge z. chem. Physiologie, **5**, 277 (1904).

in n/100 sodium hydroxid solution gained 5.08 times its weight, one in n/50 solution, 11.82 times its weight, and one in n/10 solution, 12.61 times its weight of water.

When the effect of equinormal solutions of different alkalies is compared, it is found that a gelatin disc swells more in some alkalies than in others. This statement, which has its analogue in the acids, is illustrated in Fig. 10. The hydroxids show the following grouping, in which that which allows of the greatest swelling is placed first:

Potassium, Sodium, Calcium, Ammonium.

At the concentrations employed, the electrolytic dissociation of the first three is about the same. The conclusion, therefore, seems justified that the swelling of gelatin in various alkalies

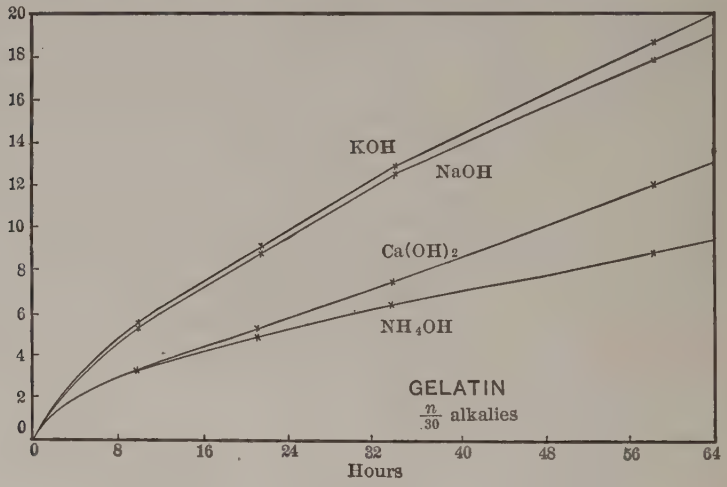


FIGURE 10.

is not solely determined by the concentration of the hydroxyl ions, but perhaps by these *minus* the effect of the kation, calcium being more active in bringing about a reduction in swelling than sodium, and this more than potassium. Fig. 10 has been constructed from the data contained in Table XVIII. As the increase in weight in these experiments on gelatin is very large, uselessly cumbersome figures have been avoided by expressing changes in weight in *parts* of the original weight of the (dry) gelatin. One part, therefore, corresponds to an increase in weight of 100 per cent.

TABLE XVIII

GELATIN—*Alkali*

Dry weight of gelatin disc.	0.830	0.830	0.830	0.822
Solution.	150 cc. n/30 KOH.	150 cc. n/30 NaOH.	150 cc. n/30 $Ca(OH)_2$.	150 cc. n/30 NH_4OH.
Hours in the solution.	Gain in parts of one part of gelatin.			
10.05	5.5	5.3	3.4	3.4
21.25	8.9	8.7	5.2	5.0
34.25	12.8	12.5	7.4	6.8
58.20	18.6	17.7	11.9	8.8

As in the case of hydrochloric acid, we find with potassium hydroxid also that the amount of swelling is dependent in a complex way upon the concentration of the alkali. This is well shown in the curve marked KOH in Fig. 9, copied from OSTWALD. It indicates the amount of water absorbed by gelatin discs after twenty-four hours residence in various concentrations of potassium hydroxid. The initial rise in the curve indicates how with an increase in the concentration of the alkali there is an increase in the amount of swelling; but, as with the acid, an optimal point is soon reached beyond which a further increase in the concentration of the potassium hydroxid leads to a diminished absorption of water.

If the amounts that gelatin will swell in equinormal solutions of acids and alkalies are compared, it is found that gelatin swells somewhat *less* in the solution of an alkali than in an equally concentrated acid. This fact, which is the reverse of that found for fibrin, is well illustrated in Fig. 9 and in the upper two curves of Fig. 8, copied from OSTWALD'S studies. It finds a ready explanation, it seems to me, in the experiments which follow. Commercial gelatin is distinctly acid. When placed in the solution of an alkali, a salt is therefore formed, the presence of which, as the next paragraph shows, markedly decreases the amount that gelatin will swell in any acid or alkaline liquid.

(*c*) The addition of any salt to the solution of an acid or an alkali decreases the amount that a gelatin disc will swell in that solution. As the number of insoluble hydroxids is large, studies on the antagonism between acids or alkalies and salts were carried out chiefly with acid solutions. Fig. 11, as well as Figs. 12, 13, 14,

15, 16, 17 and 18, illustrates this point. In Fig. 11 is compared the swelling of a gelatin disc in a pure hydrochloric acid solution, with the swelling of gelatin discs placed in equally concentrated hydrochloric acid solutions to which have been added equimolar amounts of various ammonium salts. As clearly evident, the amount of swelling is in every instance much less in these solutions

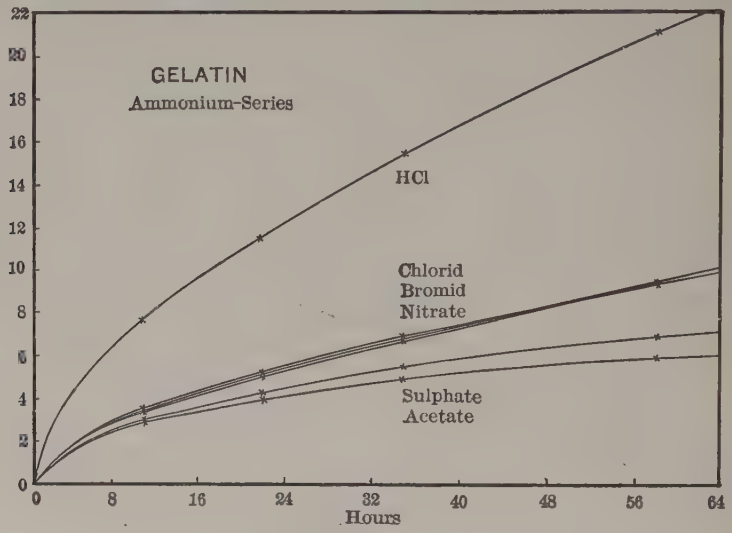


FIGURE 11.

than in the pure hydrochloric acid. Fig. 11 has been constructed from the data contained in Table XIX.

TABLE XIX

GELATIN—*Acid+Salt*

Dry weight of gelatin disc.	0.802	0.806	0.813	0.814	0.817	0.817
Solution.	50 cc. n/10 HCl+50 cc. H_2O.	50 cc. n/10 HCl+50 cc. m/2 ammonium acetate.	50 cc. n/10 HCl+50 cc. m/2 ammonium bromid.	50 cc. n/10 HCl+50 cc. m/2 ammonium chlorid.	50 cc. n/10 HCl+50 cc. m/2 ammonium nitrate.	50 cc. n/10 HCl+50 cc. m/2 ammonium sulphate.
Hours in the solution.	Gain in parts of one part of gelatin.					
10.25	7.6	2.8	3.3	3.4	3.2	2.9
21.25	11.4	3.9	5.0	5.2	4.9	4.2
34.25	15.3	4.8	6.7	6.9	6.6	5.3
58.20	21.0	5.8	9.5	9.3	9.5	6.9

The higher the concentration of the added salt, the less does the gelatin swell, and if enough is added the effect of the acid or alkali may be almost entirely suppressed. This fact is brought

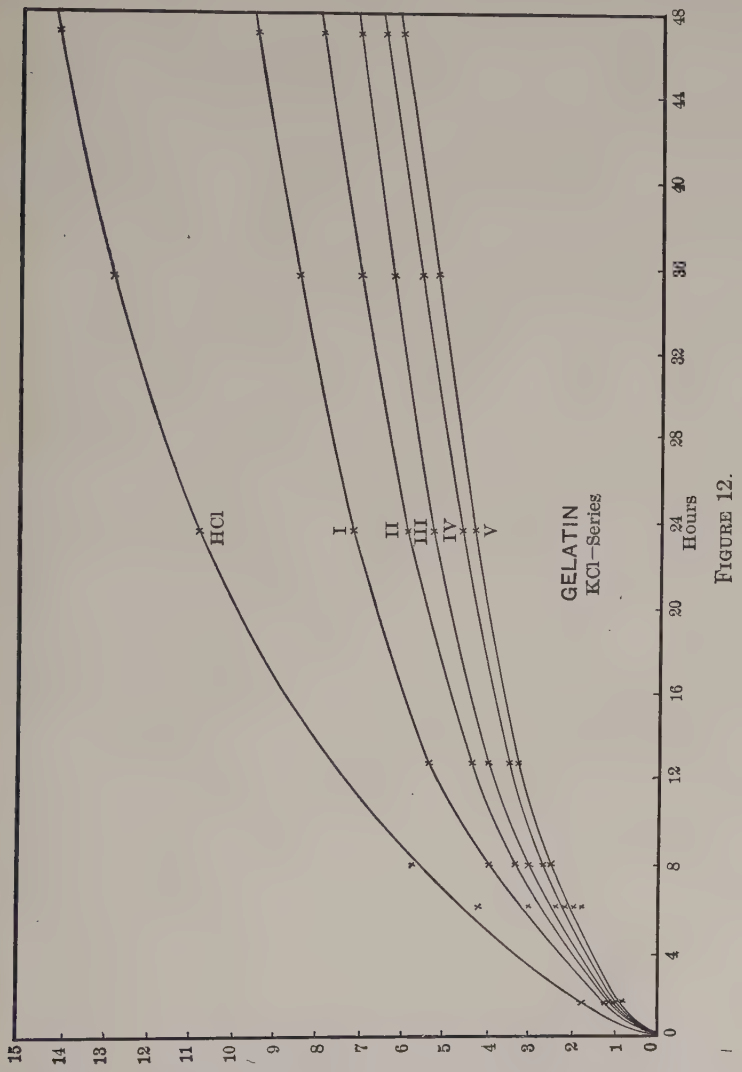


FIGURE 12.

out in Figs. 12, 13, 14, 15, 16 and 17. In each of these figures the curve for the swelling of the gelatin disc is found to lie nearer the base line with every increase in the concentration of salt employed.

(*d*) When the action of equimolar salt solutions on the swelling of gelatin discs in acid or alkaline solutions is compared, it is found that some salts depress the amount of swelling more

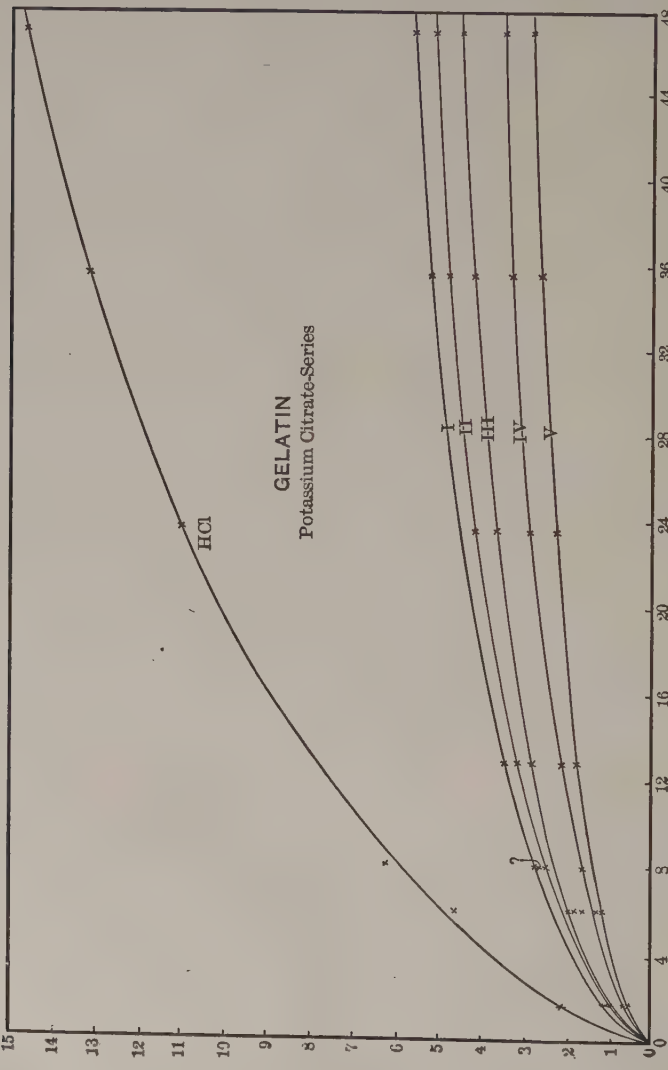


FIGURE 13.

than others. This is already apparent in Fig. 11, in which the sulphate and acetate of ammonium have brought about a distinctly greater inhibition in swelling than the chlorid, bromid

and nitrate. The point is further illustrated by comparing with each other Figs. 12, 13, and 14; also Figs. 15, 16, and 17. The hydrochloric acid curves of Figs. 12, 13, and 14 are practically

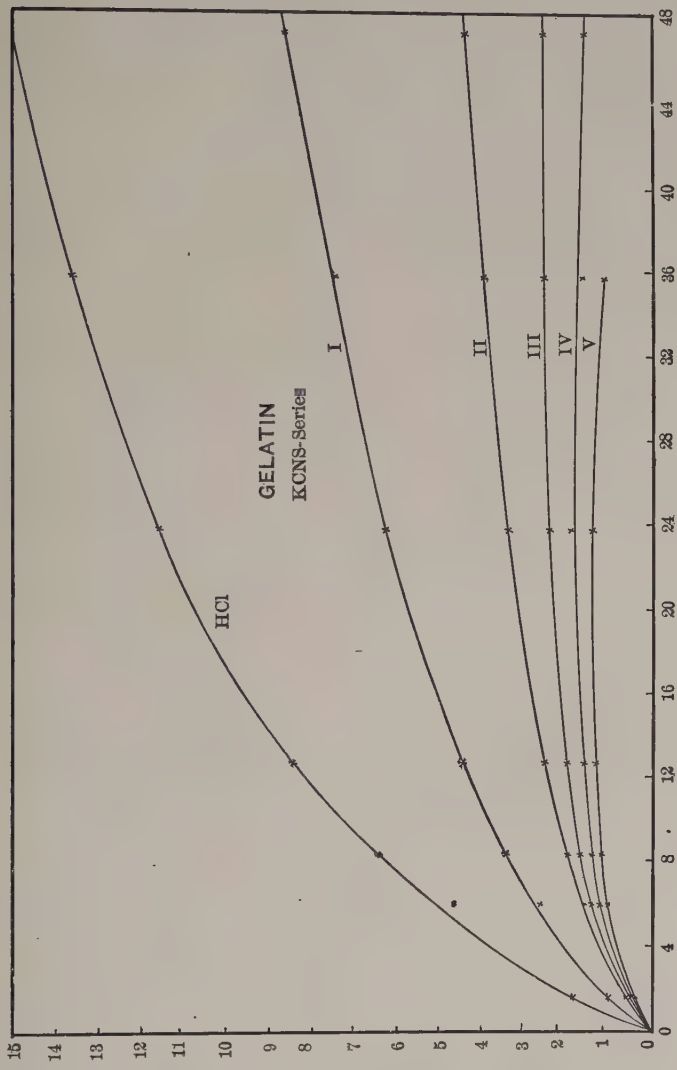


FIGURE 14.

identical. In all the figures a diminution in the amount of swelling is apparent through the addition of the salts, and the more salt added, the greater is this diminution. When Fig. 12 is com-

pared with Fig. 13, it is readily apparent that at the same concentration potassium citrate brings about a greater depression of swelling in an acid solution than potassium chlorid. When, now, we compare Fig. 14 with Fig. 12 we note that potassium sulphocyanate acts more powerfully than potassium chlorid. When we compare Fig. 13 with Fig. 14 we find that the extremes of the potassium citrate series lie between the extremes of the potassium sulphocyanate series. We cannot, in consequence, give an exact table indicative of the order in which the various acid radicals of salts with a common base are active in depressing the amount that gelatin will swell in an acid solution without stating the exact concentrations used.

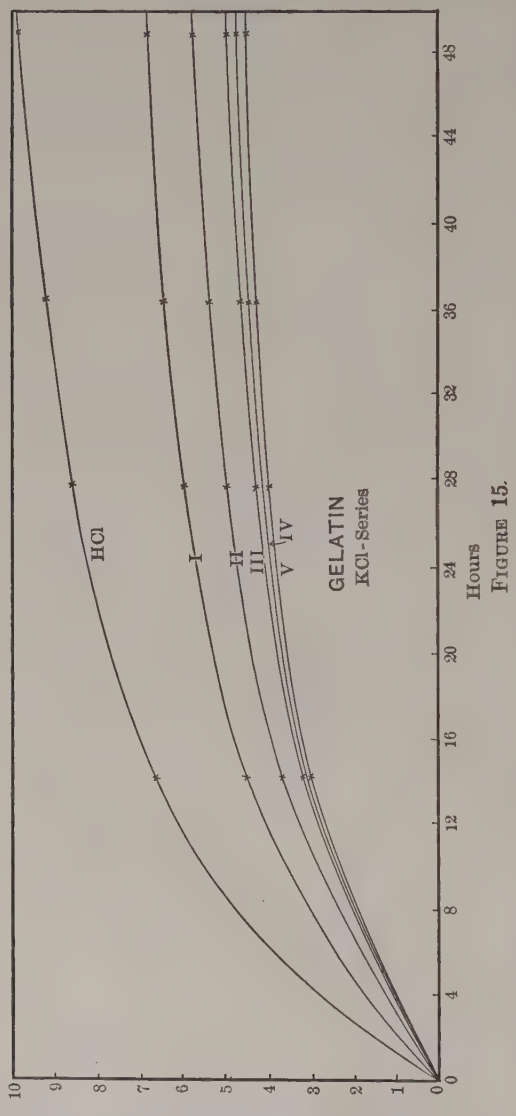


FIGURE 15.

Figs. 15, 16 and 17 permit a comparison of various basic radicals.

When Figs. 15 and 16 are compared, it is readily apparent that calcium chlorid is more effective in inhibiting the swelling

of gelatin in an acid solution than in potassium chlorid. All the curves of Fig. 16 (with the exception of the pure hydrochloric acid curve) lie distinctly below the corresponding curves in Fig. 15.[1] If we make a little allowance for experimental errors we are probably safe in saying that the curves for sodium chlorid in Fig. 17 occupy a position between those given for potassium chlorid and calcium chlorid. As the acid radical is the same in these salts, the differences may be attributed to the effect of the basic radicals which assume the following familiar order in which that least effective in reducing the swelling of gelatin is placed first.

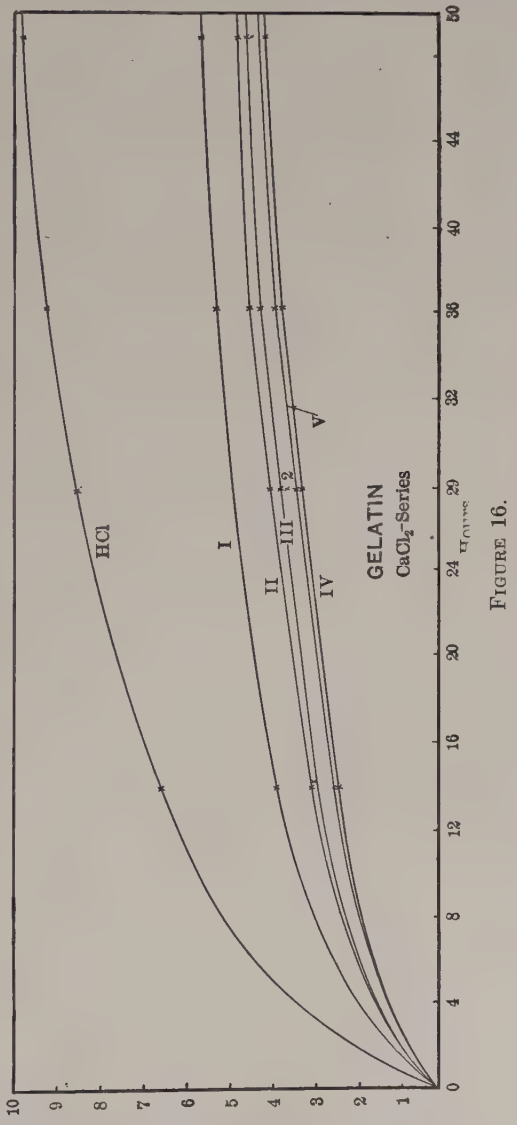


FIGURE 16.

Potassium, Sodium, Calcium

As the concentrations of acids and salts employed

[1] That curve V in Fig. 16 lies above IV represents an experimental error. The dry gelatin disc used for curve V was not as heavy as that used for curve IV. Thin discs swell faster.

are the same in the experiments from which Figs. 12 and 15 (the two potassium chlorid series) have been constructed, the question arises why the curves in the latter lie lower than those in the former. The gelatin and all external conditions were the same in these two sets of experiments except the temperature, and it is to the higher temperature prevailing when the experiments of Figs. 12, 13 and 14 were carried out (September 4 to 7,1908) than when those of Figs. 15, 16 and 17 were made (November 11 to 20, 1908), that I attribute the marked absolute differences in the amount of the swelling.

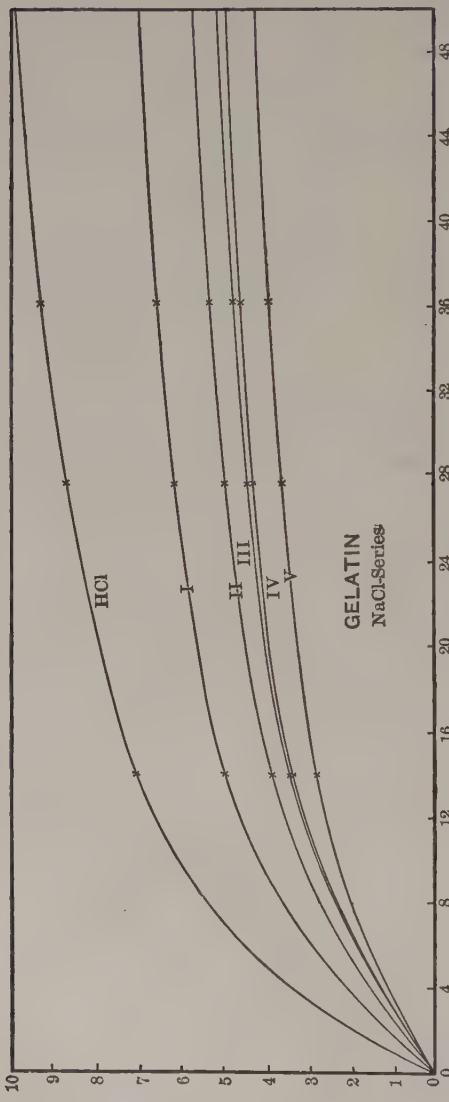


FIGURE 17.

A point that we will find of biological interest later is well brought out in Figs. 12 to 17. This is the amount of inhibition in the swelling with any unit increase in the concentration of the added salt. *It is clearly evident that to double the concentration of the salt is not to double the diminution in swelling—in every case the diminution is less than might be expected.*

In Fig. 18 is illustrated the effect of adding equimolar solutions of different sodium salts to a solution of sodium hydroxid. It is easily seen how much more powerfully the citrate, phosphate, tartrate and sulphate interfere with the swelling of the gelatin discs in this alkaline solution, than the various univalent acid radicals. *The general grouping of the salts as to the way in which*

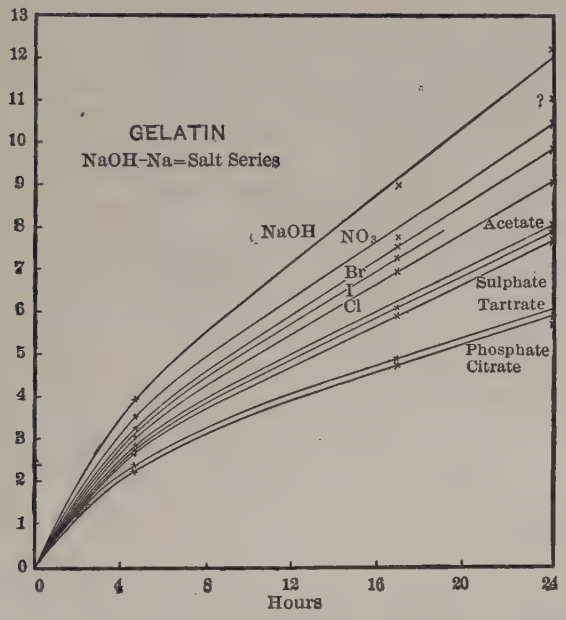


FIGURE 18.

they affect the swelling of gelatin in solutions of acids and alkalies is therefore the same as that discovered in our study of the swelling of fibrin.

Tables XX, XXI, XXII, XXIII, XXIV, XXV and XXVI contain the experimental data from which have been constructed, respectively, Figs, 12, 13, 14, 15, 16, 17 and 18.

TABLE XX

GELATIN—*Acid+Salt*

Dry wt. of gelatin disc.	0.800	0.802	0.803	0.809	0.810	0.813
Solution.	50 cc. n/10 HCl +40 cc. H_2O +10 cc. m/1 potassium chlorid.	50 cc. n/10 HCl +30 cc. H_2O +20 cc. m/1 potassium chlorid.	50 cc. n/10 HCl +20 cc. H_2O +30 cc. m/1 potassium chlorid.	50 cc. n/10 HCl +10 cc. H_2O +40 cc. m/1 potassium chlorid.	50 cc. n/10 HCl +50 cc. m/1 potassium chlorid.	50 cc. n/10 HCl +50 cc. H_2O.
Hrs. in the solution.	Gain in parts of one part of gelatin.					
1.40	1.36	1.21	1.21	1.03	1.00	1.81
6.05	3.02	2.49	2.39	2.05	1.87	4.26
8.05	4.11	3.42	3.17	2.75	2.53	5.86
12.40	5.41	4.48	4.06	3.57	3.32	6.63
23.35	7.27	6.01	5.40	4.66	4.48	10.82
35.25	8.56	7.06	6.34	5.67	5.29	12.79
47.05	9.58	8.01	7.21	6.51	6.11	14.16
	I	II	III	IV	V	

TABLE XXI

GELATIN—*Acid+Salt*

Dry wt. of gelatin disc.	0.763	0.765	0.766	0.772	0.775	0.778
Solution.	50 cc. n/10 HCl +40 cc. H_2O +10 cc. m/1 potassium citrate.	50 cc. n/10 HCl +30 cc. H_2O +20 cc. m/1 potassium citrate.	50 cc. n/10 HCl +20 cc. H_2O +30 cc. m/1 potassium citrate.	50 cc. n/10 HCl +10 cc. H_2O +40 cc. m/1 potassium citrate.	50 cc. n/10 HCl +50 cc. m/1 potassium citrate.	50 cc. n/10 HCl +50 cc. H_2O.
Hrs. in the solution.	Gain in parts of one part of gelatin.					
1.40	1.11	1.01	0.95	0.73	0.61	2.20
6.05	1.93	1.86	1.68	1.25	1.02	4.55
8.05	2.64	2.46	2.61 (?)	1.64	1.33	6.22
12.40	3.39	3.13	2.81	2.08	1.65	6.93
23.35	4.42	4.04	3.63	2.80	2.21	11.13
35.25	5.12	4.67	4.15	3.26	2.56	13.13
47.05	5.57	5.09	4.52	3.59	2.84	14.61
	I	II	III	IV	V	

TABLE XXII

GELATIN—*Acid+Salt*

Dry wt. of gelatin disc.	0.778	0.782	0.783	0.788	0.790	0.794
Solution.	50 cc. n/10 HCl+40 cc. H_2O+10 cc. m/1 potassium sulpho-cyanate.	50 cc. n/10 HCl+30 cc. H_2O+20 cc. m/1 potassium sulpho-cyanate.	50 cc. n/10 HCl+20 cc. H_2O+30 cc. m/1 potassium sulpho-cyanate.	50 cc. n/10 HCl+10 cc. H_2O+40 cc. m/1 potassium sulpho-cyanate.	50 cc. n/10 HCl+50 cc. m/1 potassium sulpho-cyanate.	50 cc. n/10 HCl+50 cc. H_2O.
Hrs. in the solution.	Gain in parts of one part of gelatin.					
1.40	1.33	0.86	0.82	0.73	0.68	2.06
6.05	2.68	1.54	1.40	1.25	1.07	4.61
8.05	3.46	1.96	1.65	1.32	1.16	6.27
12.40	4.47	2.54	1.93	1.47	1.18	8.43
23.35	6.28	3.36	2.42	1.85	1.43	11.49
35.25	7.50	3.93	2.56	1.56	1.11	13.58
47.05	8.74	4.56	2.66	1.56	Too sticky to weigh	15.07
	I	II	III	IV	V	

TABLE XXIII

GELATIN—*Acid+Salt*

Dry wt. of gelatin disc.	0.755	0.792	0.755	0.771	0.722	0.750
Solution.	50 cc. n/10 HCl+40 cc. H_2O+10 cc. m/1 potassium chlorid.	50 cc. n/10 HCl+30 cc. H_2O+20 cc. m/1 potassium chlorid.	50 cc. n/10 HCl+20 cc. H_2O+30 cc. m/1 potassium chlorid.	50 cc. n/10 HCl+10 cc. H_2O+40 cc. m/1 potassium chlorid.	50 cc. n/10 HCl+50 cc. m/1 potassium chlorid.	50 cc. n/10 HCl+50 cc. H_2O.
Hrs. in the solution.	Gain in parts of one part of gelatin.					
14.00	4.5	3.7	3.2	3.2	3.0	6.5
27.35	5.9	4.9	4.2	4.0	3.8	8.6
36.15	6.4	5.3	4.6	4.5	4.2	9.2
48.45	6.8	5.8	5.0	4.8	4.6	9.8
75.35	7.5	6.3	5.8	5.6	5.3	11.0
144.15	9.2	7.9	7.0	6.9	6.4	12.9
213.15	10.3	8.9	7.8	7.7	7.2	14.4
	I	II	III	IV	V	

TABLE XXIV

GELATIN—*Acid+Salt*

Dry wt. of gelatin disc.	0.724	0.743	0.723	0.788	0.738	0.740
Solution.	50 cc. n/10 HCl +40 cc. H_2O +10 cc. m/1 calcium chlorid.	50 cc. n/10 HCl +30 cc. H_2O +20 cc. m/1 calcium chlorid.	50 cc. n/10 HCl +20 cc. H_2O +30 cc. m/1 calcium chlorid.	50 cc. n/10 HCl +10 cc. H_2O +40 cc. m/1 calcium chlorid.	50 cc. n/10 HCl +50 cc. m/1 calcium chlorid.	50 cc. n/10 HCl +50 cc. H_2O.
Hrs. in the solution.	Gain in parts of one part of gelatin.					
14.00	3.8	2.9	2.9	2.3	2.4	6.5
27.35	3.5	3.9	3.7	3.2	3.4	8.4
36.15	5.3	4.4	4.2	3.7	3.9	9.2
48.45	5.6	4.7	4.6	4.1	4.4	9.7
75.35	6.4	5.5	5.4	5.0	5.4	10.9
144.15	7.6	6.8	6.8	6.8	7.4	12.9
213.15	8.5	7.6	7.8	7.9	8.7	14.6
	I	II	III	IV	V	

TABLE XXV

GELATIN—*Acid+Salt*

Dry wt. of gelatin disc.	0.632	0.690	0.686	0.597	0.700	0.676
Solution.	50 cc. n/10 HCl +40 cc. H_2O +10 cc. m/1 sodium chlorid.	50 cc. n/10 HCl +30 cc. H_2O +20 cc. m/1 sodium chlorid.	50 cc. n/10 HCl +20 cc. H_2O +30 cc. m/1 sodium chlorid.	50 cc. n/10 HCl +10 cc. H_2O +40 cc. m/1 sodium chlorid.	50 cc. n/10 HCl +50 cc. m/1 sodium chlorid.	50 cc. n/10 HCl +50 cc. H_2O.
Hrs. in the solution.	Gain in parts of one part of gelatin.					
14.00	5.0	3.9	3.5	3.5	2.8	7.1
27.35	6.2	4.9	4.4	4.3	3.6	8.7
36.15	6.6	5.3	3.5 (?)	4.6	3.9	9.3
48.45	7.0	5.7	5.1	4.9	4.2	9.8
75.35	7.8	6.3	5.6	5.4	4.8	10.8
144.15	9.1	7.6	6.9	6.5	5.9	12.7
213.15	10.0	8.4	7.5	6.9	6.6	14.2
	I	II	III	IV	V	

TABLE XXVI

GELATIN—*Alkali+Salt*

Dry wt. of gelatin disc.	0.799	0.798	0.797	0.787	0.782
Solution.	50 cc. n/10 NaOH +50 cc. H_2O.	50 cc. n/10 NaOH +50 cc. m/5 sodium acetate.	50 cc. n/10 NaOH +50 c. m/5 sodium bromid.	50 cc. n/10 NaOH +50 cc. m/5 sodium chlorid.	50 cc. n/10 NaOH+50cc. m/5 sodium citrate.
Hrs. in the solution.	Gain in parts of one part of gelatin.				
4.45	3.94	2.71	3.37	3.14	2.22
17.00	8.83	6.00	7.42	6.91	4.73
24.30	12.38	8.12	9.83	9.29	6.23
47.30	melted	too soft to weigh	too soft to weigh	too soft to weigh	8.65 much broken

Dry wt. of gelatin disc.	0.776	0.770	0.756	0.755	0.754
Solution.	50 cc. n/10 NaOH +50 cc. m/5 sodium iodid.	50 cc. n/10 NaOH +50 cc. m/5 sodium nitrate.	50 cc. n/10 NaOH +50 cc. m/5 disodium phosphate.	50 cc. n/10 NaOH +50 cc. m/5 sodium sulphate.	50 cc. n/10 NaOH+50cc. m/5 NaK tartrate.
Hrs. in the solution.	Gain in parts of one part of gelatin.				
4.45	3.34	3.46	2.41	2.95	2.88
17.00	7.40	7.58	4.78	6.04	5.95
24.30	11.02	10.40	6.10	8.08	7.82
47.30	melted	almost melted	9.11 good body	breaks on handling	firmer than preceding

(*e*) Non-electrolytes do not share with electrolytes their marked power of reducing through their presence the amount that gelatin will swell in the solution of any acid or alkali. Figs. 19, 20 and 21 illustrate this better than words. The upper curve of Fig. 19 indicates the amount and rate of swelling of a gelatin disc in a pure hydrochloric acid solution. The *black* circles, crosses, squares and triangles just below this curve give the gains in weight of gelatin discs kept in equally concentrated hydrochloric acid solutions to which various amounts of ethyl alcohol have been added. While present in amounts *osmotically* more than equivalent to the salts added in the previously described experiments, there is practically no reduction in the amount of swelling of the gelatin discs. The same is true when methyl

alcohol is added to a hydrochloric acid solution. To avoid confusion only one of these curves has been filled in, and the

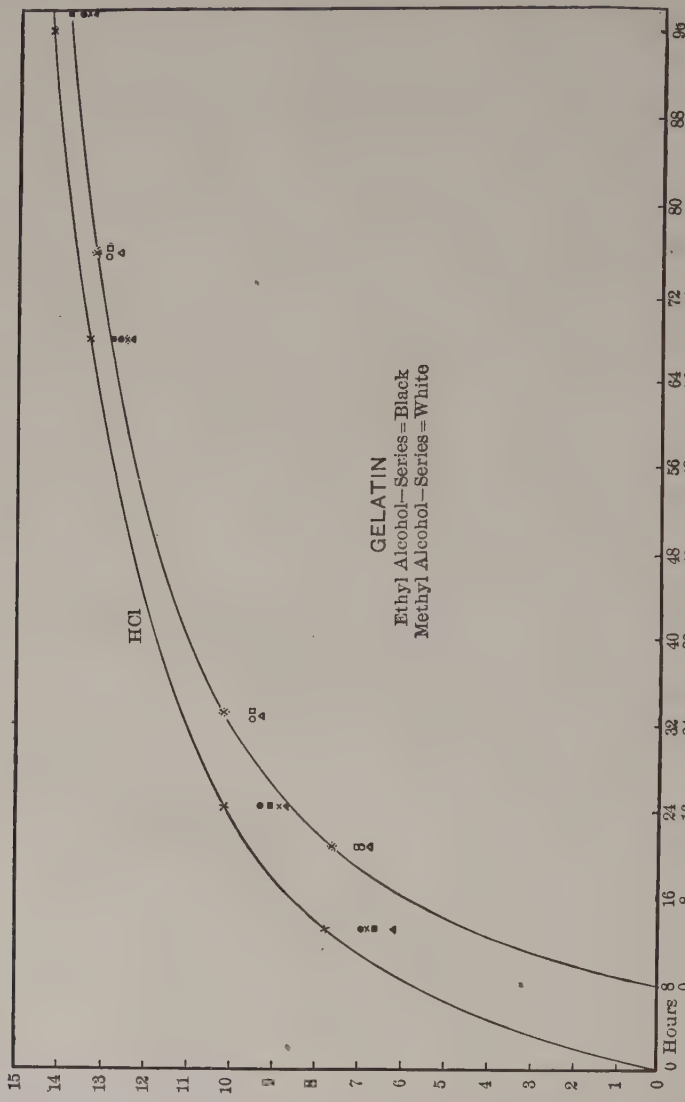


FIGURE 19.

whole series has been placed somewhat to the right in the drawing. The methyl alcohol series is indicated in *white* crosses, squares, circles and triangles to distinguish it from the ethyl alcohol

series. As readily apparent, the characters practically coincide with each other.

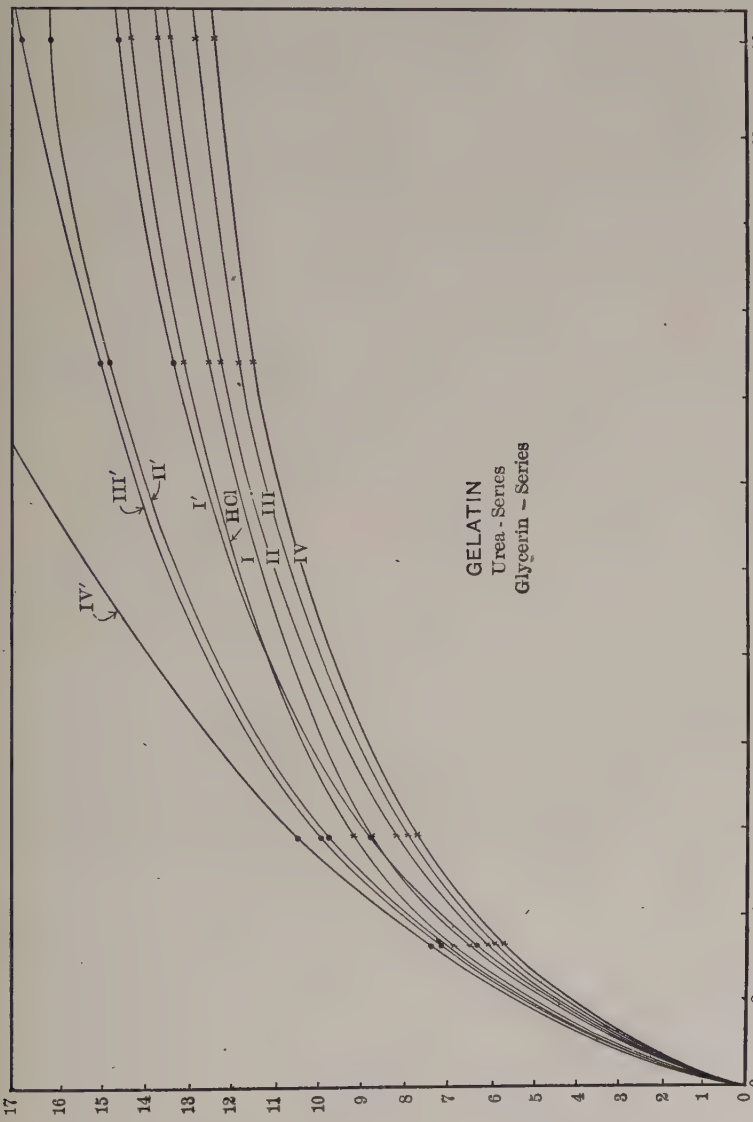


FIGURE 20.

In Fig. 20 is shown the effect of adding various amounts of glycerin and urea to a hydrochloric acid solution. The curve

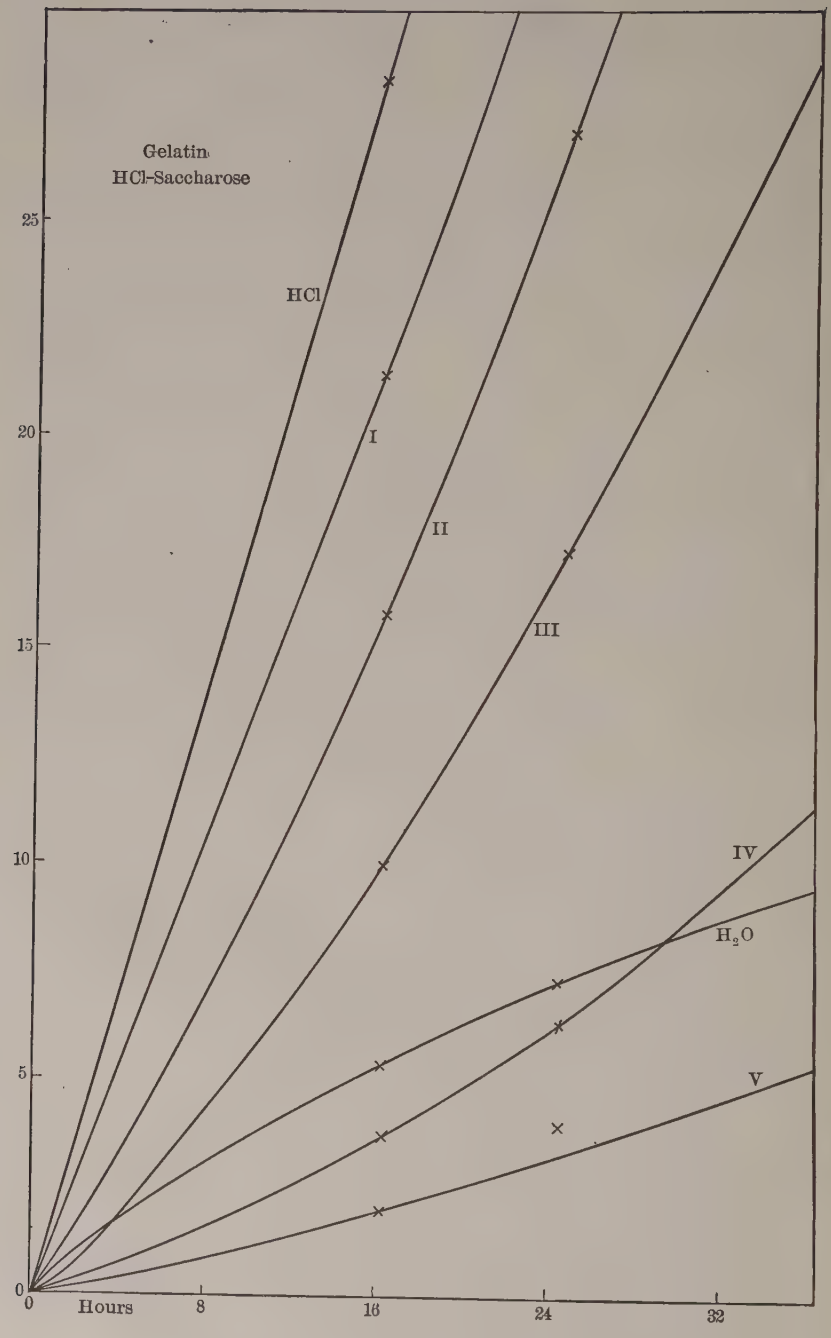

Gelatin
HCl-Saccharose
HCl
I
II
III
IV
H_2O
V
25
20
15
10
5
0
0
Hours
8
16
24
32

FIGURE 21.

for the pure hydrochloric acid solution occupies a position at about the middle of the series. The curves marked I, II, III and IV show the effect on swelling of adding progressively larger amounts of glycerin to the hydrochloric acid solution. Glycerin produces a definite decrease in the amount of swelling, though as compared with the effect of any electrolyte, it is slight. Urea, on the other hand, distinctly *favors* the swelling of gelatin in a hydrochloric acid solution, and this the more the higher the concentration of the urea. The curves marked I′, II′, III′ and IV′ demonstrate this fact.

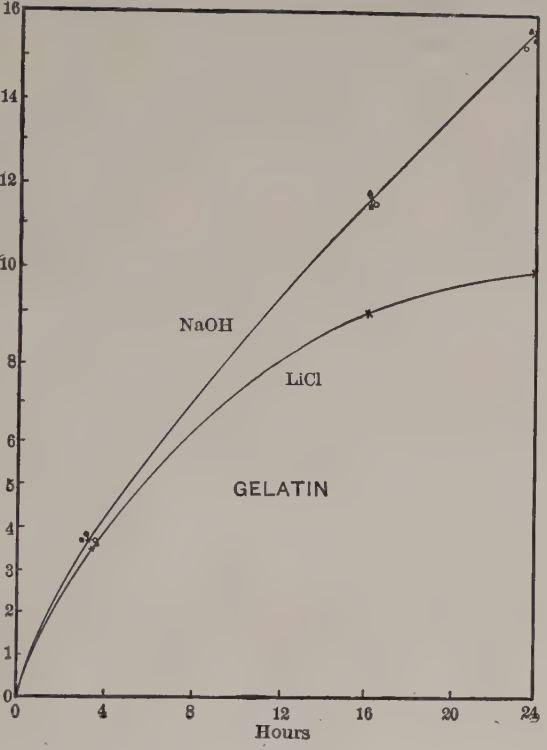


FIGURE 22.

Because the non-electrolytes are so *comparatively* ineffective in reducing the swelling of protein colloids in the presence of an acid many have made this statement read, *entirely* without effect. This is by no means the case, a fact which must be remembered for future discussion. The various sugars, for example, have, like glycerin, a decided dehydrating effect, especially in the higher concentrations. Fig. 21 illustrates this in the case of saccharose, which represents the most active of this class of compounds.

The effect of various non-electrolytes on the swelling of gelatin in an *alkaline* solution is shown in Fig. 22. Only the curve for the pure sodium hydroxid has been filled in. As with acids, urea again favors the swelling. The addition of ethyl and methyl

alcohols and glycerin is without effect, for these curves practically coincide with that for the pure alkali. In contrast hereto the addition of an electrolyte, lithium chlorid, produces a distinct diminution in the amount of the swelling.

The curves of Figs. 19, 20, 21 and 22 have been constructed from the experimental data contained in Tables XXVII, XXVIII XXIX and XXX respectively.

TABLE XXVII

GELATIN—*Acid+Non-electrolytes*

Dry wt. of gelatin disc.	0.773	0.765	0.756	0.748	0.723
Solution.	50 cc. n/10 HCl+40 cc. H_2O+10 cc. 2/m ethyl alcohol.	50 cc. n/10 HCl+30 cc. H_2O+20 cc. 2/m ethyl alcohol.	50 cc. n/10 HCl+20 cc. H_2O+30 cc. 2/m ethyl alcohol.	50 cc. n/10 HCl+50 cc. 2/m ethyl alcohol.	50 cc. n/10 HCl+50 cc. H_2O.
Hrs. in the solution.	Gain in parts of one part of gelatin.				
13.20	6.9	6.7	6.8	6.2	7.7
24.45	9.2	9.1	8.8	8.7	10.1
67.30	12.5	12.7	12.4	12.3	13.2
97.05	13.5	13.8	13.5	13.4	14.2
113.35	13.8	14.1	13.9	13.9	14.6
162.45	14.4	14.7	14.5	14.4	15.1
212.05	14.7	15.0	14.8	14.7	15.5
13 days	15.4 Black Circle	15.6 Black Square	15.3 Black Cross	15.0 Black Triangle	16.2

Dry wt. of gelatin disc.	0.733	0.729	0.727	0.724
Solution.	50 cc. n/10 HCl+40 cc. H_2O+10 cc. 2/m methyl alcohol.	50 cc. n/10 HCl+30 cc. H_2O+20 cc. 2/m methyl alcohol.	50 cc. n/10 HCl+20 cc. H_2O+30 cc. 2/m methyl alcohol.	50 cc. n/10 HCl+50 cc. 2/m methyl alcohol.
Hrs. in the solution.	Gain in parts of one part of gelatin.			
13.20	7.6	6.9	7.1	6.7
24.45	10.1	9.4	9.4	9.2
67.30	13.1	12.7	12.7	12.5
97.05	14.0	13.7	13.7	13.5
113.35	14.4	13.9	14.1	13.9
162.45	14.9	14.6	14.6	14.3
212.05	15.4	14.9	14.9	14.1
13 days	16.0 White Star	15.5 White Circle	15.4 White Square	15.2 White Triangle

TABLE XXVIII

GELATIN—*Acid+Non-electrolytes*

Dry wt. of gelatin disc.	0.829	0.872	0.842	0.816	0.810
Solution.	50 cc. n/10 HCl +40 cc. H_2O +10 cc. 2/m glycerin.	50 cc. n/10 HCl +50 cc. H_2O +20 cc. 2/m glycerin.	50 cc. n/10 HCl +20 cc. H_2O +30 cc. 2/m glycerin.	50 cc. n/10 HCl +50 cc. 2/m glycerin.	50 cc. n/10 HCl +50 cc. H_2O.
Hrs. in the solution.	Gain in parts of one part of gelatin.				
13.20	6.6	6.1	5.9	5.6	6.9
24.45	9.0	8.2	8.1	7.8	9.4
67.30	12.5	12.2	11.7	11.4	13.1
97.05	13.6	13.3	12.8	12.4	14.2
113.35	13.9	13.7	13.1	12.7	14.6
162.45	14.5	14.3	13.7	13.2	15.2
212.05	14.8	14.6	14.0	13.5	15.6
13 days	15.3 I	15.1 II	14.5 III	14.0 IV	17.0

Dry wt. of gelatin disc.	0.851	0.848	0.837	0.832
Solution.	50 cc. n/10 HCl +40 cc. H_2O +10 cc. 2/m urea.	50 cc. n/10 HCl +30 cc. H_2O +20 cc. 2/m urea.	50 cc. n/10 HCl +20 cc. H_2O +30 cc. 2/m urea.	50 cc. n/10 HCl +50 cc. 2/m urea.
Hrs. in the solution.	Gain in parts of one part of gelatin.			
13.20	6.4	7.2	7.2	7.3
24.45	9.1	10.1	10.2	10.8
67.30	13.3	14.7	15.0	18.1
97.05	14.5	16.1	16.7	20.7
113.35	15.1	16.6	17.3	21.5
162.45	15.7	17.4	18.4	23.1
212.05	16.0	17.7	18.8	23.7
13 days	16.8 I′	18.6 II′	19.5 III′	24.5 V′

(*f*) For purposes of biological application there are introduced here a series of experiments showing the effect of various non-electrolytes upon ordinary commercial gelatin when no acid or alkali has been added from without.[1]

No special comments are necessary upon the results reproduced in this paper, obtained by comparing the swelling of gelatin in water with the swelling of this same gelatin in differently con-

[1] MARTIN H. FISCHER and ANNE SYKES: Science, **38**, 486 (1913); Kolloid-Zeitschr., **14**, 215 (1914).

centrated solutions of various non-electrolytes. We used saccharose, levulose, dextrose, methyl alcohol, propyl alcohol,

TABLE XXIX

GELATIN—*Acid+Saccharose*

Dry wt. of gelatin disc.	0.518	0.515	0.515	0.507	0.502	0.501	0.500
Solution.	100 cc. H_2O	5 cc. n/10 HCl +95 cc. H_2O	5 cc. n/10 HCl + 5 cc. 2/m saccharose +90 cc. H_2O	5 cc. n/10 HCl +30 cc. 2/m saccharose +65 cc. H_2O	5 cc. n/10 HCl +50 cc. 2/m saccharose +45 cc. H_2O	5 cc. n/10 HCl +75 cc. 2/m saccharose +20 cc. H_2O	5 cc. n/10 HCl +95 cc. 2/m saccharose
Hrs. in the Solution.	Gain in parts of one part of gelatin.						
18.45	5.28	28.36	21.38	15.90	9.72	3.62	1.89
26.30	6.27	47.54	41.71	31.90	17.27	7.18	3.98
42.00	9.88	In sol	ution	58.17	36.25	13.50	6.08
50.45	12.26	.....	.....	65.07	51.75	17.50	7.78

TABLE XXX

GELATIN—*Alkali+Non-electrolytes*

Dry wt. of gelatindisc.	0.710	0.712	0.714	0.715	0.716	0.705
Solution.	50 cc. n/10 NaOH +50 cc. m/5 LiCl.	50 cc. n/10 NaOH +50 cc. 2/5 m urea.	50 cc. n/10 NaOH +50 cc. 2/5 m glycerin.	50 cc. n/10 NaOH +50 cc. 2/5 m ethyl alcohol.	50 cc. n/10 NaOH +50 cc. 2/5 m methyl alcohol.	50 cc. n/10 NaOH +50 cc. H_2O.
Hrs. in the solution.	Gain in parts of one part of gelatin.					
3.15	3.46	3.70	3.71	3.70	3.64	3.80
16.15	9.07	12.45	11.53	11.79	11.51	11.70
24.00	9.98	13.57 Melting Black circle	15.79 White circle	15.29 Triangle	15.60 Square	15.82

propylene glycol and acetone. The presence of all these non-electrolytes reduces the amount of the swelling, and this the more the higher the concentration of the added substance.

When these curves are paralleled with those available on the effect of different electrolytes (salts) on the swelling of gelatin

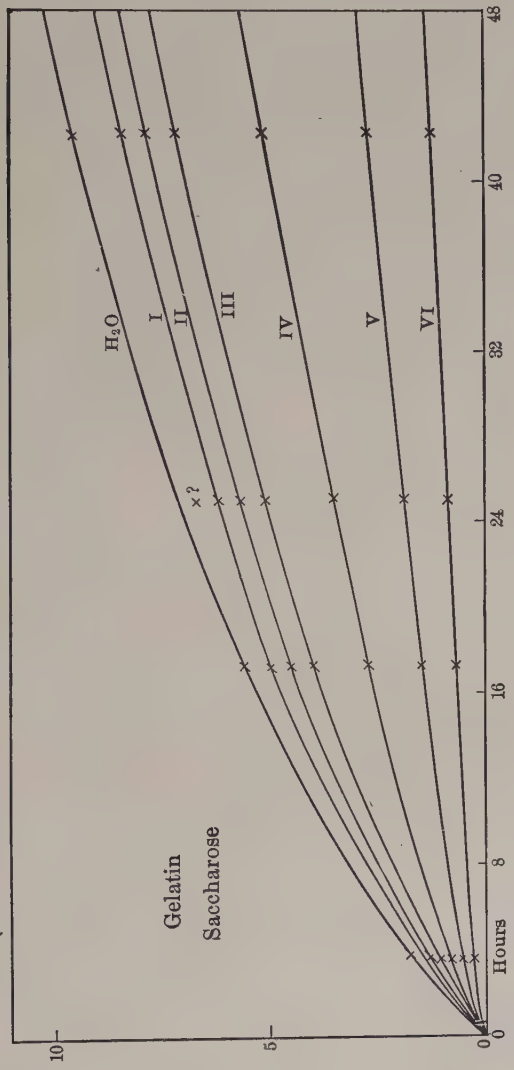


FIGURE 23.

in the presence of acid one is impressed with the fact, when equimolar or osmotically equivalent solutions are compared, that the non-electrolytes are relatively most powerful in their de-

hydrating effects in the higher concentrations, while of the electrolytes the reverse is true. Thus, in even low concentrations

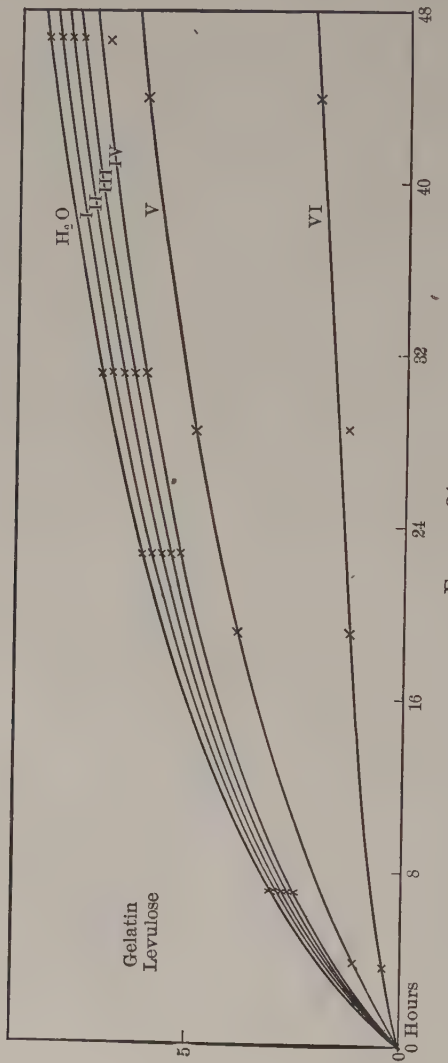


FIGURE 24.

the salts produce a great dehydrating effect, but with every unit increase in concentration the degree of shrinkage becomes progressively less. Just the opposite holds for the non-electrolytes,

where low concentrations are comparatively ineffective, but where an unexpectedly great dehydrating effect is observed as the concentration rises.

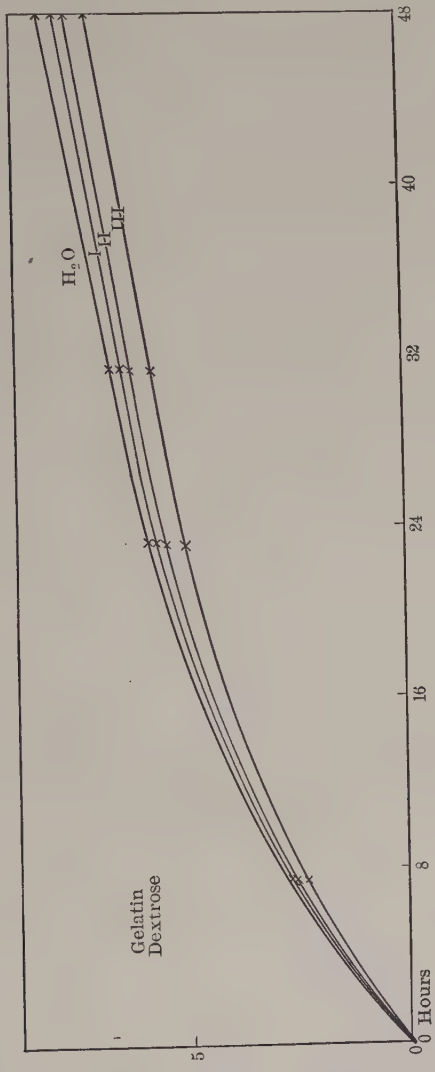


FIGURE 25.

But while all these non-electrolytes reduce the swelling of gelatin there exist some interesting quantitative differences between them. As shown in Figs. 23, 24 and 25 and the corre-

TABLE XXXI

GELATIN—*Saccharose*

Dry wt. of gelatin disc.	0.726	0.721	0.722	0.723	0.724	0.725	0.726
Solution.	100 cc. H_2O	10 cc. 2/m saccharose +90 cc. H_2O	20 cc. 2/m saccharose +80 cc. H_2O	30 cc. 2/m saccharose +70 cc. H_2O	50 cc. 2/m saccharose +50 cc. H_2O	75 cc. 2/m saccharose +25 cc. H_2O	100 cc. 2/m saccharose
Hrs. in the Solution.	Gain in parts of one part of gelatin						
2.45	1.51	0.81	1.13	1.03	0.78	0.52	0.26
17.15	5.61	5.03	4.56	4.01	2.69	1.43	0.65
25.00	6.65	6.11	5.59	4.97	3.41	1.76	0.90
42.15	9.51	8.29	7.83	7.21	5.18	2.65	1.15
65.15	11.69	9.36	9.34	8.74	6.51	3.53	1.54

TABLE XXXII

GELATIN—*Levulose*

Dry wt. of gelatin disc.	0.732	0.744	0.750	0.759	0.797		0.797	0.797
Solution.	100 cc. H_2O	10 cc. 2/m levulose +90 cc. H_2O	20 cc. 2/m levulose +80 cc. H_2O	30 cc. 2/m levulose +70 cc. H_2O	50 cc. 2/m levulose +50 cc. H_2O		100 cc. 2/m levulose	100 cc. 4/m levulose
Hrs. in the solution.	Gain in parts of one part of gelatin. Hours.							
7.00	2.90	2.90	2.78	2.71	2.55	3.50	1.16	0.46
22.30	6.01	5.80	5.67	5.38	5.29	19.00	3.74	1.13
31.00	6.77	6.47	6.25	6.23	6.03	28.20	4.89	1.43
46.30	8.44	7.97	7.87	7.71	6.82	43.50	7.24	2.11
55.00	8.77	8.07	8.17	8.11	8.27			

TABLE XXXIII

GELATIN—*Dextrose*

Dry weight of gelatin disc.	0.678	0.699	0.699	0.713
Solution.	100 cc. H_2O	10 cc. 2/m dextrose +90 cc. H_2O	20 cc. 2/m dextrose +80 cc. H_2O	30 cc. 2/m dextrose +70 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.			
7.30	2.44	2.76	2.75	2.27
23.15	5.85	5.82	5.61	4.97
31.15	6.51	6.46	6.31	5.71
47.15	8.26	8.09	7.92	7.29
55.45	8.72	8.19	8.17	7.62

sponding Tables XXXI, XXXII and XXXIII, the various sugars all reduce the swelling of gelatin, but at the same con-

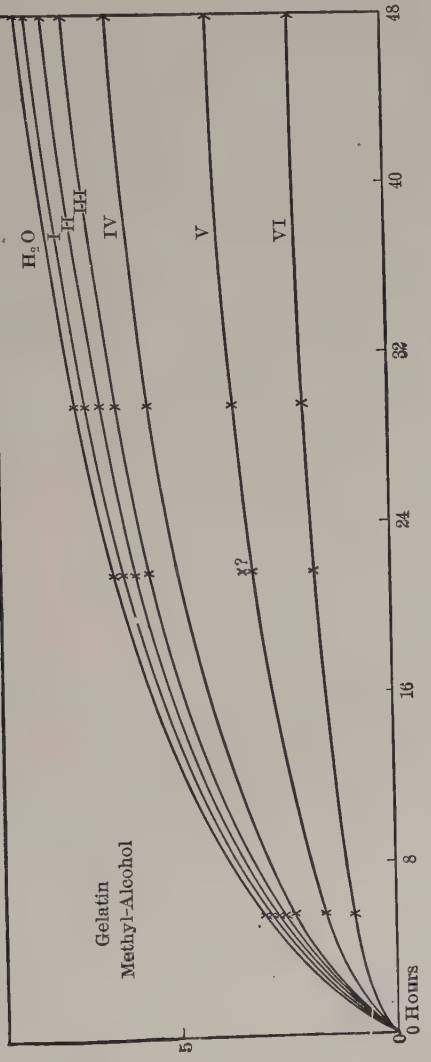


FIGURE 26.

centration saccharose is far more powerful in this regard than either levulose or dextrose, which produce approximately equal

degrees of dehydration. This is readily apparent on comparing curves I, II, III, IV and VI of Fig. 23 with the corresponding

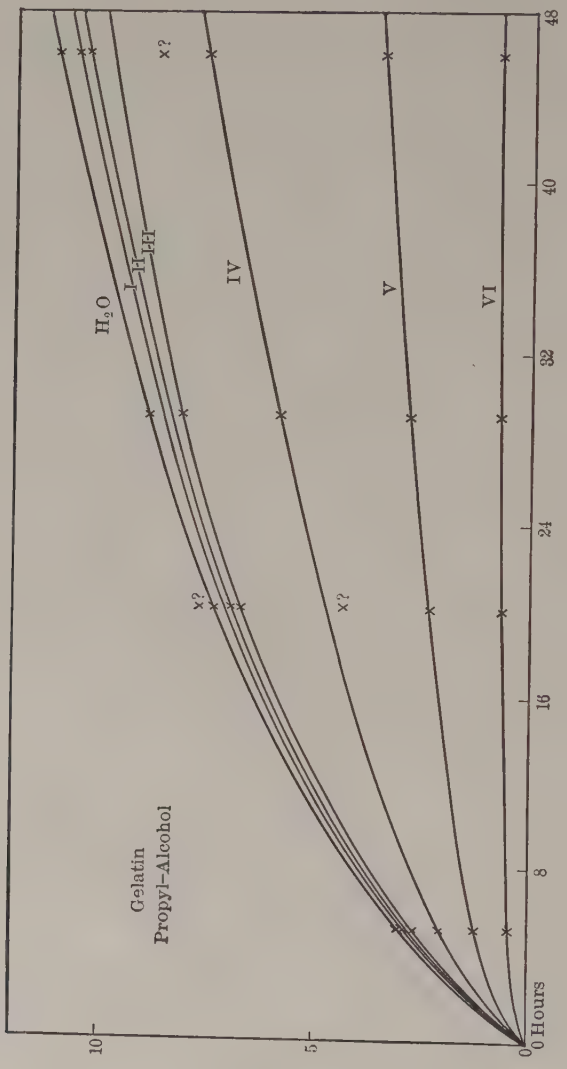


FIGURE 27.

curves I, II, III, IV and V of Fig. 24, or the first three of these with curves I, II and III of Fig. 25.

Methyl and propyl alcohols, propylene glycol and acetone

all approximate the monosaccharids in the degree of dehydration which they bring about. Only in very high concentra-

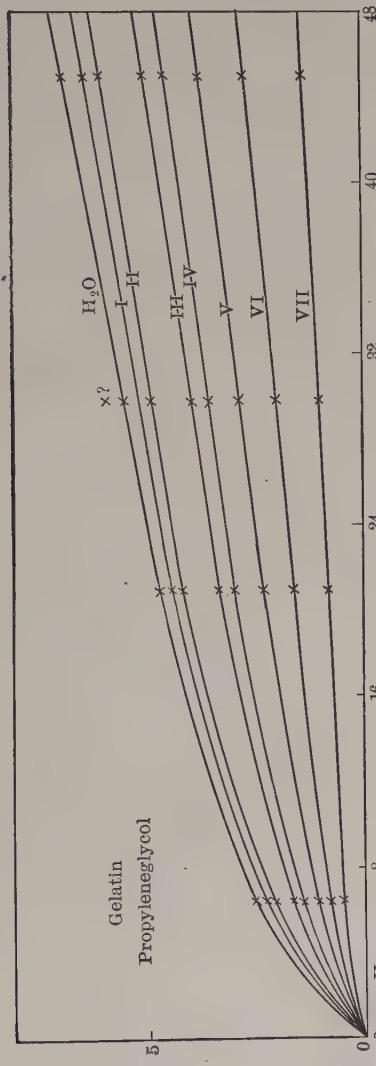


FIGURE 28.

tions are they able to bring about a dehydration which saccharose brings about in much lower ones, as readily apparent when Figs. 26, 27, 28 and 29 are compared with Fig. 23.

Tables XXXIV, XXXV, XXXVI and XXXVII contain the experimental data from which Figs. 26 to 29 have been constructed.

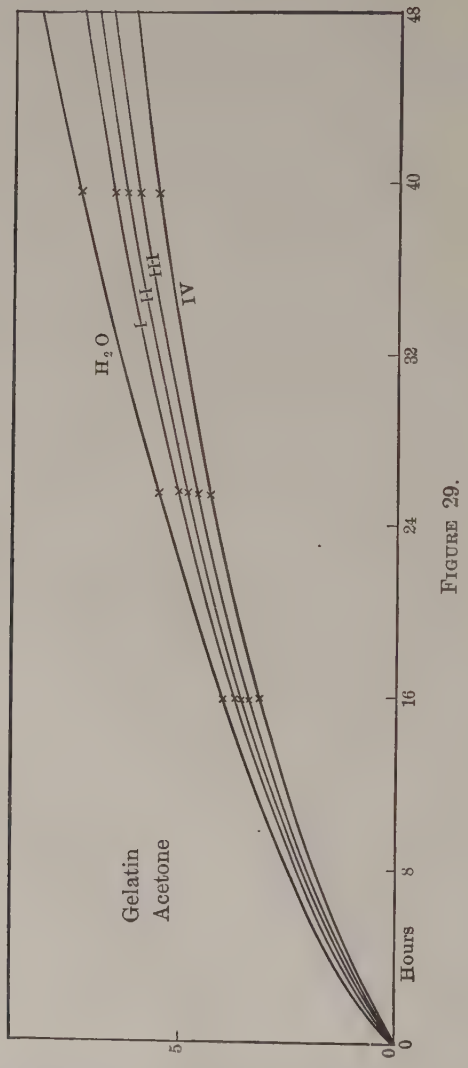


FIGURE 29.

(*g*) The absorption and secretion of water by gelatin represent in large part reversible processes. This fact is brought out in

TABLE XXXIV

GELATIN—*Methyl Alcohol*

Dry weight of gelatin disc.	0.747	0.729	0.729	0.739	0.744	0.746	0.746
Solution.	100 cc. H_2O	2 cc. 10/m methyl alcohol +98 cc. H_2O	5 cc. 10/m methyl alcohol +95 cc. H_2O	10 cc. 10/m methyl alcohol +90 cc. H_2O	20 cc. 10/m methyl alcohol +80 cc. H_2O	50 cc. 10/m methyl alcohol +50 cc. H_2O	100 cc. 10/m methyl alcohol
Hours in the solution.	Gain in parts of one part of gelatin.						
5.30	2.95	2.85	2.57	2.55	2.36	1.60	0.93
21.30	6.32	6.27	5.87	5.50	3.15	3.12	1.69
29.30	7.12	7.01	6.63	6.27	5.50	3.58	1.97
48.00	8.54	8.30	7.83	7.43	6.45	4.09	2.14
53.30	9.52	8.21	8.39	7.87	6.76	4.29	2.19

TABLE XXXV

GELATIN—*Propyl Alcohol*

Dry weight of gelatin disc.	0.708	0.681	0.683	0.683	0.689	0.690	0.707
Solution.	100 cc. H_2O	2 cc. 10/m propyl alcohol +98 cc. H_2O	5 cc. 10/m propyl alcohol +95 cc. H_2O	10 cc. 10/m propyl alcohol +90 cc. H_2O	20 cc. 10/m propyl alcohol +80 cc. H_2O	50 cc. 10/m propyl alcohol +50 cc. H_2O	100 cc. 10/m propyl alcohol
Hours in the solution.	Gain in parts of one part of gelatin.						
5.00	2.85	2.72	2.59	2.46	2.08	1.19	0.28
20.00	7.28	7.51	7.21	6.74	4.25	2.15	0.51
29.00	8.71	8.85	8.83	8.07	5.70	2.75	0.55
46.00	11.16	10.39	10.37	8.54	7.61	3.43	0.58

Fig. 30 and Table XXXVIII, from which it is constructed. When a gelatin disc is transferred from a pure hydrochloric acid or sodium hydroxid solution into an equally concentrated one containing a salt, a prompt fall in the absorption curve is noted. A rise in the curve follows the reverse process. A further fact of interest in Fig. 30 is that at the same concentration potassium citrate inhibits the swelling of gelatin in a hydrochloric acid solution more than in an equinormal sodium hydroxid solution.

TABLE XXXVI

GELATIN—*Propylene Glycol*

Dry wt. of gelatin disc.	0.718	0.755	0.752	0.748	0.747	0.743	0.733	0.709
Solution.	100 cc. H_2O	2 cc. 10/m propylene glycol +98 cc. H_2O	5 cc. 10/m propylene glycol +95 cc. H_2O	10 cc. 10 m propylene glycol +90 cc. H_2O	20 cc. 10/m propylene glycol +80 cc. H_2O	30 cc. 10/m propylene glycol +70 cc. H_2O	50 cc. 10/m propylene glycol +50 cc. H_2O	80 cc. 10/m propylene glycol +20 cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.							
6.15	2.49	2.19	2.07	1.59	1.36	1.09	0.89	0.40
20.45	4.60	4.49	4.36	3.43	3.06	2.32	1.61	0.74
29.45	5.30	5.98	4.85	3.91	3.53	2.85	1.79	0.92
45.00	6.82	6.26	6.11	4.97	4.59	3.72	2.86	1.43
54.30	7.33	7.14	6.69	5.47	5.00	4.04	3.17	1.46

TABLE XXXVII

GELATIN—*Acetone*

Dry weight of gelatin disc.	0.808	0.808	0.807	0.810	0.811
Solution.	100 cc. H_2O.	2 cc. 10/m acetone +98 cc. H_2O.	5 cc. 10/m acetone +95 cc. H_2O.	10 cc. 10/m acetone +90 cc. H_2O.	20 cc. 10/m acetone +80 cc. H_2O.
Hours in the solution.	Gain in parts of one part of gelatin.				
16.00	4.06	3.72	3.56	3.37	3.18
25.30	5.59	5.05	4.99	4.78	4.28
39.30	7.49	6.55	6.48	6.15	5.78
49.15	8.39	7.43	7.20	6.69	6.10
66.00	10.39	9.27	8.44	7.57	6.60

(*h*) There are other substances besides acids which will increase the amount of water that gelatin can hold. First to be mentioned are the salts of the alkali metals. As first noted by FRANZ HOFMEISTER such salts as the chlorids, bromids and iodids of sodium, potassium and lithium increase the absorption of water by pure gelatin. This matter is verified for sodium chlorid in Fig. 31 and Table XXXIX, which contains the experimental details. In paragraph (*e*) above, urea was found to be a sub-

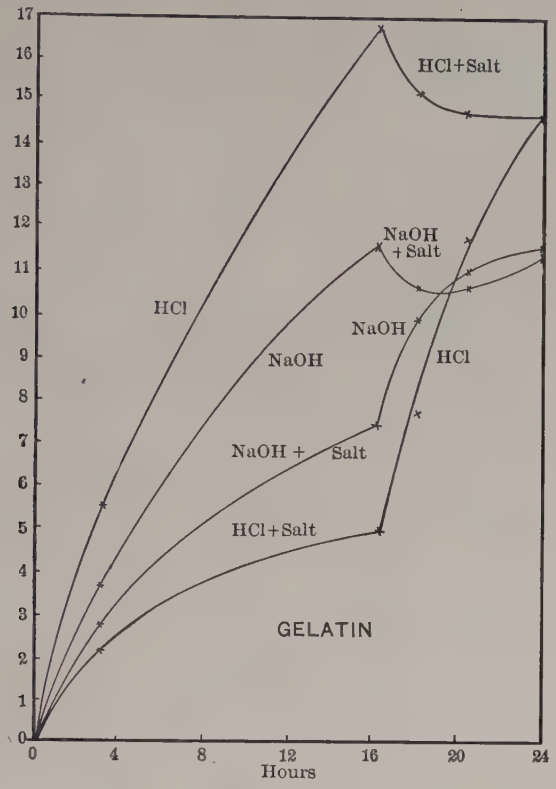


FIGURE 30.

TABLE XXXVIII

GELATIN

Dry weight of gelatin disc.	I 0.705	II 0.705	III 0.722	IV 0.721
Solution.	50 cc. n/10 NaOH +50 cc. H_2O.	50 cc. n/10 NaOH +50 cc. m/5 K citrate.	50 cc. n/10 HCl +50 cc. H_2O.	50 cc. n/10 HCl +50 cc. m/5 K citrate.
Hours in the solution.	Gain in parts of one part of gelatin.			
3.15	3.80	2.74	5.44	2.26
16.15	11.70	7.39	16.74	5.02
	Disc I is put into Solution II; Disc II into Solution I. Disc III is put into Solution IV; Disc IV into Solution III.			
18.25	10.49	9.85	15.20	7.64
20.35	10.63	11.19	14.70	12.26
24.00	11.21	11.34	14.72	14.77

stance which when added to an acid solution would increase the swelling of gelatin. Urea will do this also in neutral solu-

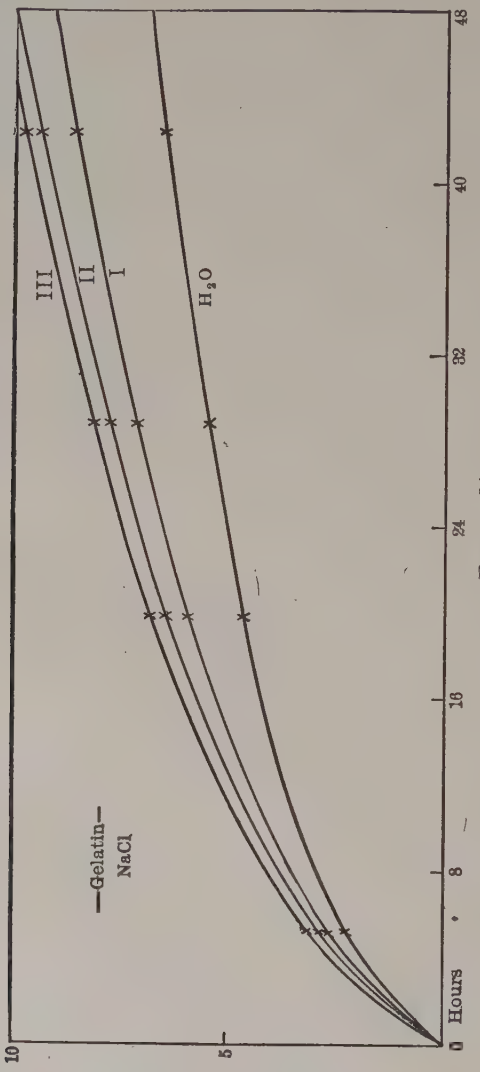


FIGURE 31.

tion as shown in Fig. 32 and Table XL, from which this is constructed. When the urea is sufficiently concentrated the gelatin goes into solution. Pyridin represents another substance which

TABLE XXXIX

GELATIN—*NaCl.*

Dry weight of gelatin disc.	0.715	0.712	0.701	0.694
Solution	100 cc. H_2O	10 cc. m/1 NaCl +75 cc. H_2O	25 cc. m/1 NaCl +75 cc. H_2O	50 cc. m/1 NaCl +50 cc. H_2O
Hours in the solution	Gain in parts of one part of gelatin			
5.30	2.43	2.83	2.98	3.12
20.30	4.59	6.04	6.54	6.91
29.30	5.26	6.71	7.33	7.77
43.30	6.68	8.60	9.59	9.60
52.00	7.32	9.19	10.20	10.12
67.00	9.02	11.47	12.60	13.67
76.00	10.98	13.31	13.70	15.08

TABLE XL

GELATIN—*Urea*

Dry weight of gelatin disc.	0.786	0.782	0.793	0.796	0.759	0.760	0.788
Solution	100 cc. H_2O	2 cc. 10/m urea +98 cc. H_2O	5 cc. 10/m urea +95 cc. H_2O	10 cc. 10/m urea +90 cc. H_2O	20 cc. 10/m urea +80 cc. H_2O	50 cc. 10/m urea +50 cc. H_2O	100 cc. 10/m urea
Hours in the solution	Gain in parts of one part of gelatin						
5.30	2.60	2.67	2.88	3.26	2.96	Complete solution	
21.45	5.93	6.83	8.17	10.65	Complete solution		
45.15	7.97	9.97	11.36	14.45			

TABLE XLI

GELATIN—*Pyridin*

Dry weight of gelatin disc.	0.780	0.780	0.781	0.783	0.783	0.783	0.784	0.785
Solution	100 cc. H_2O	0.1 cc. 5/m pyridin +100 cc. H_2O	0.2 cc. 5/m pyridin +100 cc. H_2O	0.5 cc. 5/m pyridin +100 cc. H_2O	1 cc. 5/m pyridin +99 cc. H_2O	2 cc. 5/m pyridin +98 cc. H_2O	3 cc. 5/m pyridin +97 cc. H_2O	5 cc. 5/m pyridin +95 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin							
16.45	3.75	3.77	4.01	4.10	4.44	4.63	4.84	5.00
38.45	6.12	6.43	6.73	6.98	7.59	8.56	9.85	10.40
46.30	6.51	6.87	7.23	7.51	8.22	9.28	11.77	11.52
62.30	8.00	8.48	8.96	9.16	10.12	11.91	14.19	15.63
73.00	9.29	9.61	9.85	10.45	13.23	13.48	16.60	18.38

has activities in this direction, as shown in Fig. 33 and Table XLI.

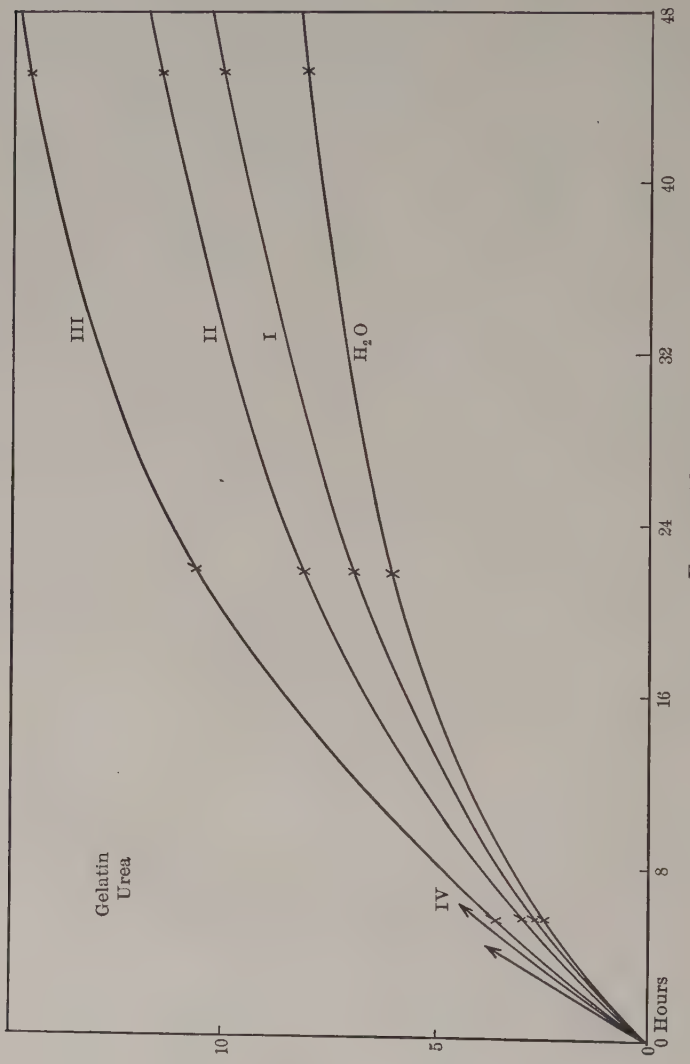


FIGURE 32.

Some of the amins also belong in the group with urea and pyridin, but they are so intensely alkaline in watery solution that special pains need to be taken to eliminate first this alkaline effect

before their more specific hydrating action becomes evident. Hans Handovsky first noted the hydrating effects of the amins

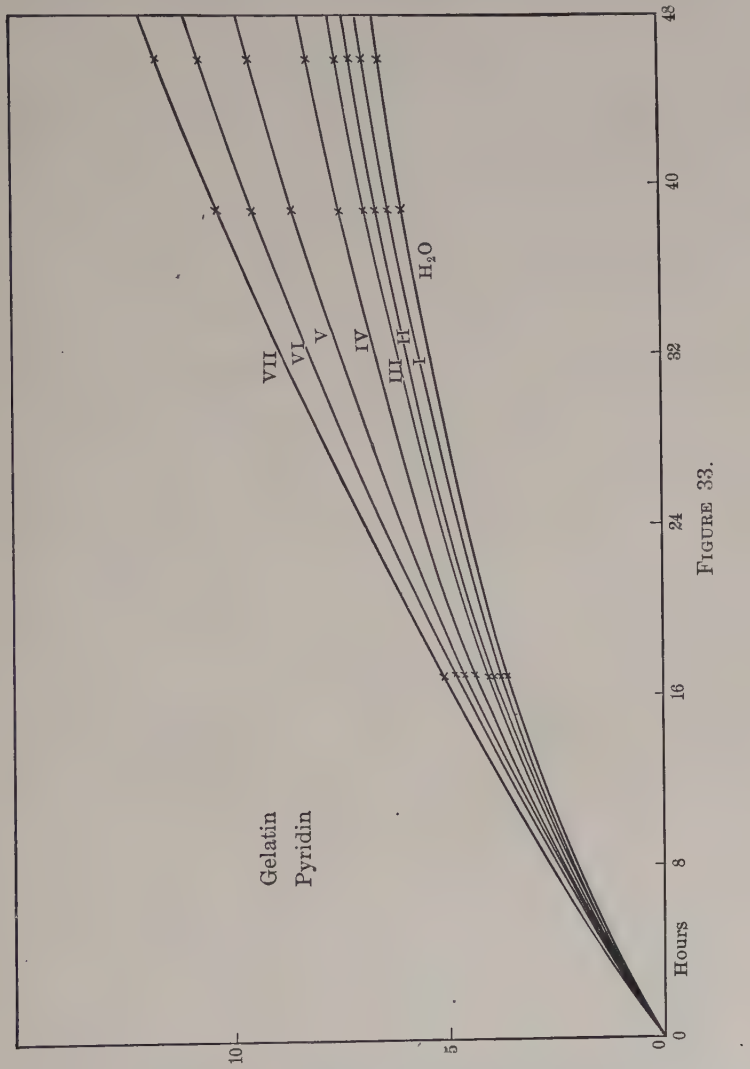


Figure 33.

upon blood proteins. The swelling effects of different concentrations of ethylamin upon gelatin are illustrated in Fig. 34 and Table XLII.

(*i*) As previously emphasized for fibrin, the hydration induced

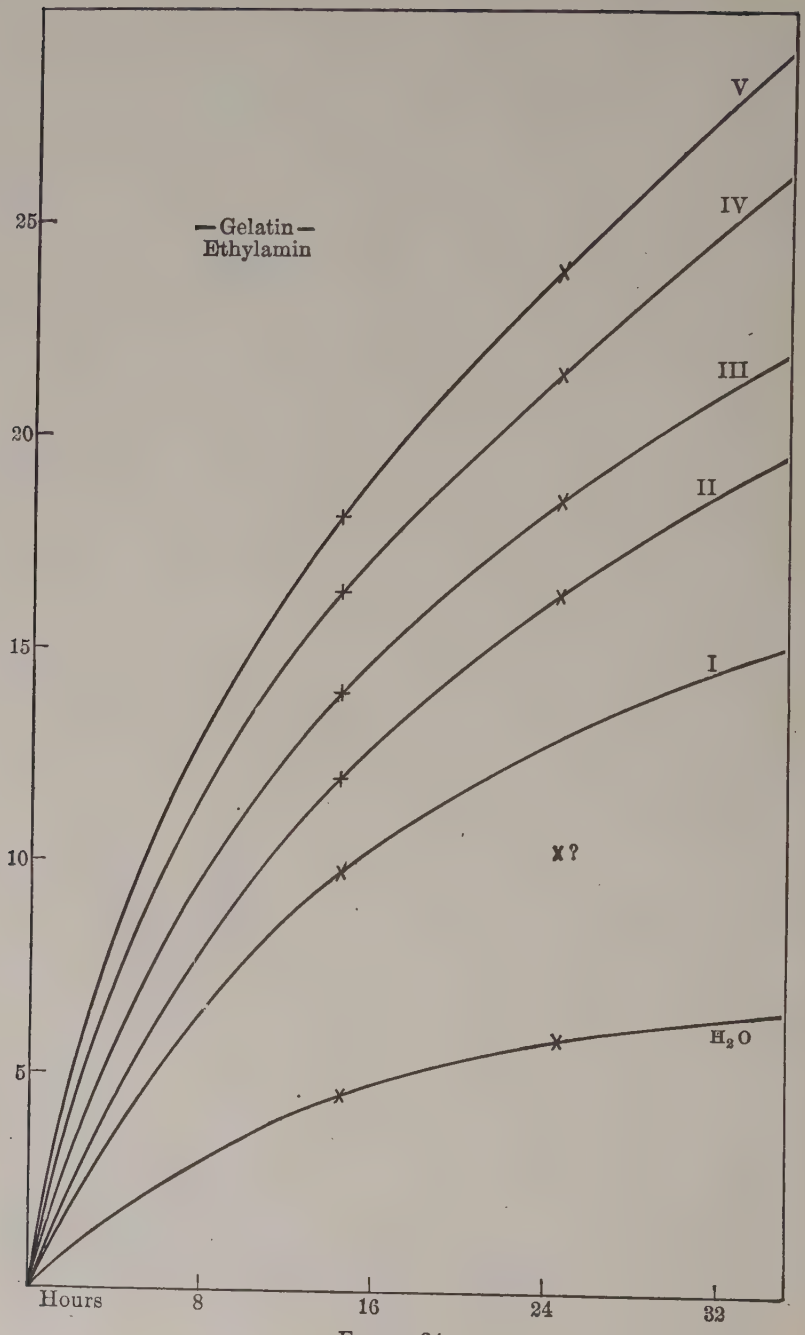

V
IV
III
II
I
—Gelatin—
Ethylamin
X?
H_2O
25
20
15
10
5
Hours
8
16
24
32

FIGURE 34.

TABLE XLII

GELATIN—*Ethylamin*

Dry weight of gelatin disc.	0.793	0.800	0.800	0.800	0.802	0.802
Solution	100 cc. H_2O	0.1 cc. 5/m ethylamin +99.9 cc. H_2O	0.2 cc. 5/m ethylamin +99.8 cc. H_2O	0.3 cc. 5/m ethylmain +99.7 cc. H_2O	0.5 cc. 5/m ethylamin +99.5 cc. H_2O	0.75 cc. 5/m ethylamin +99.25 cc. H_2O
Hours in the solution	Gain in parts of one part of gelatin					
15.00	4.80	10.25	12.26	14.76	17.66	18.85
25.00	6.04	10.56	15.83	17.93	21.10	23.25
39.00	6.25	15.67	21.30	23.15	27.66	31.72
		I	II	III	IV	V

through urea, pyridin or the amins is of a type different from that produced through (acids or) alkalies. As shown in paragraph (*e*) above and again in Fig. 35 and Table XLIII an acid does not decrease the swelling effects of urea—the effects of the two substances are compounded. The same is true for the addition of sodium chlorid to a urea solution. Instead of reducing the swelling, as would be the case did urea act merely as an alkali, Fig. 36 and Table XLIV show that the hydrating effect of pure sodium chlorid upon gelatin is merely added to that produced by urea. On the other hand, various non-electrolytes, such as the sugars, reduce a urea hydration markedly, while, as noted above, they

TABLE XLIII

GELATIN—*Urea+HCl*

Dry weight of gelatin disc.	0.553	0.553	0.556	0.557	0.558
Solution	100 cc. H_2O	20 cc. 5/m urea +80 cc. H_2O	20 cc. 5/m urea +3 cc. n/10 HCl +77 cc. H_2O	20 cc. 5/m urea +4 cc. n/10 HCl +76 cc. H_2O	20 cc. 5/m urea +5 cc. n/10 HCl +75 cc. H_2O
Hours in the solution	Gain in parts of one part of gelatin				
18.15	5.18	9.82	14.08	20.54	34.84
26.30	6.36	13.52	17.00	37.79	Complete solution
42.00	9.41	35.16	Complete solution		

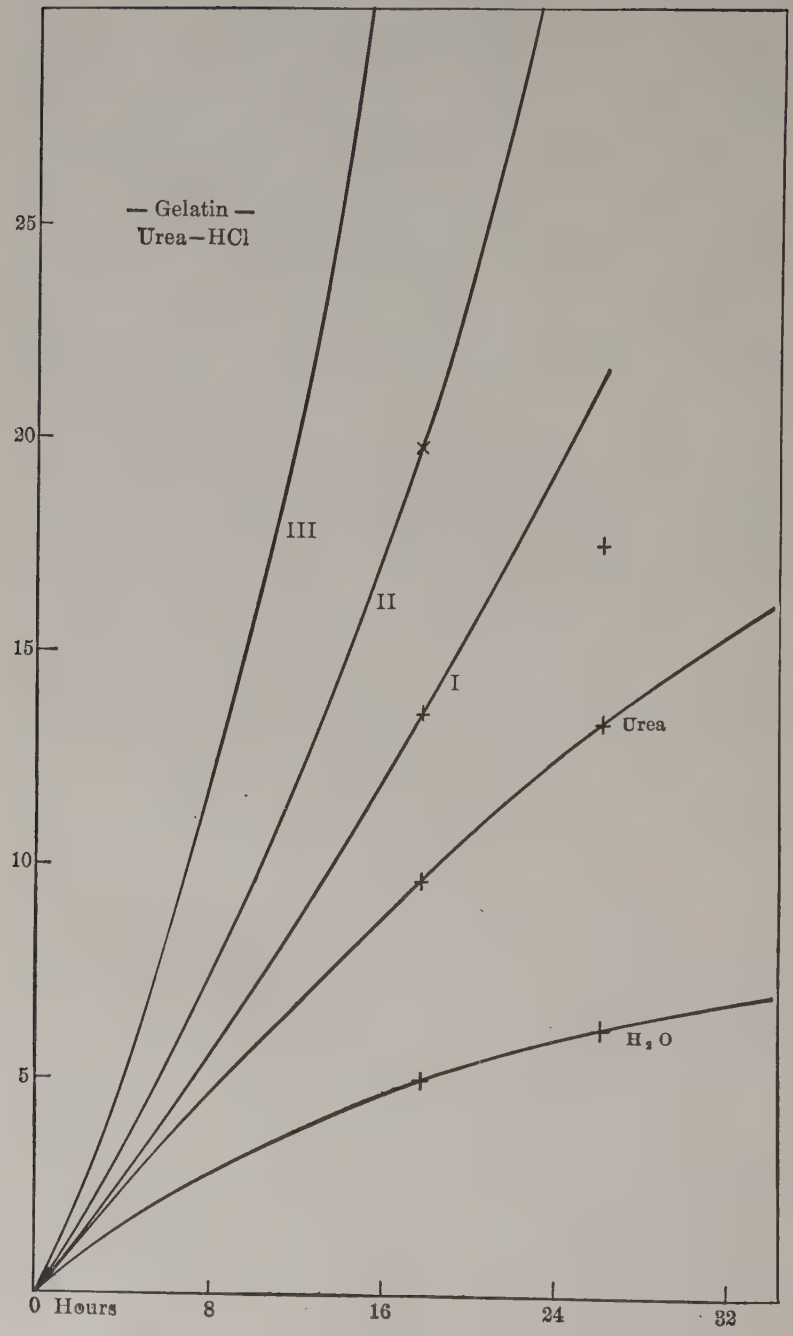


FIGURE 35.

are relatively ineffective in the case of an acid or alkali hydration. The effect of dextrose on urea hydration is illustrated in Fig. 37 and Table XLV, from which it is drawn.

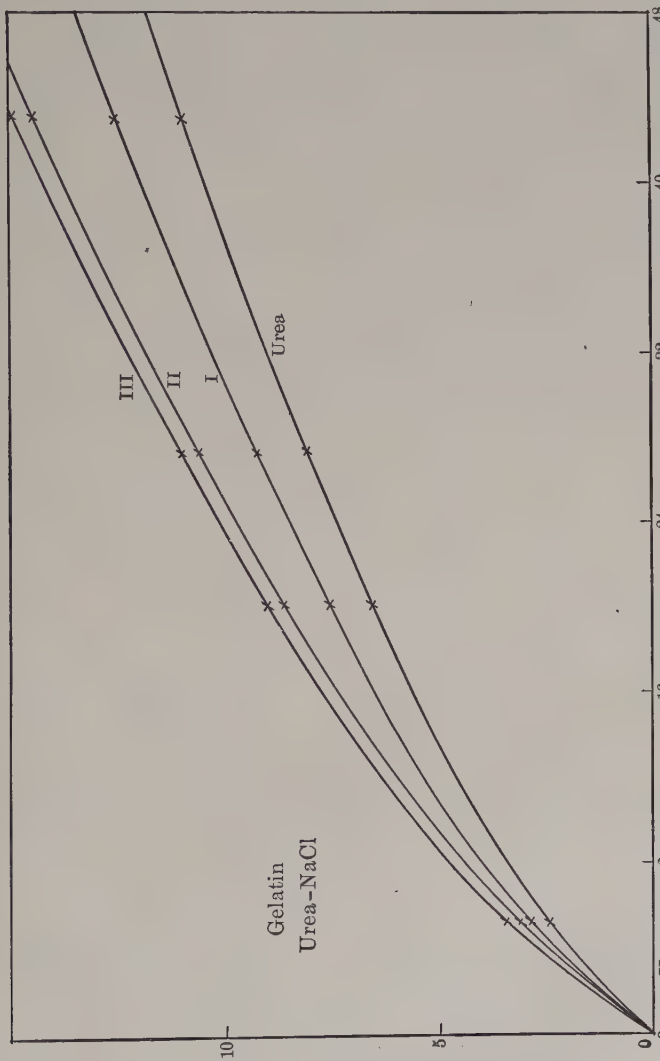


FIGURE 36.

Remarks similar to those made for urea may be made for pyridin except that pyridin shows distinctly alkaline properties. The effects of an electrolyte like sodium chlorid in reducing the

TABLE XLIV

GELATIN—*Urea+NaCl*

Dry weight of gelatin disc.	0.792	0.787	0.786	0.773
Solution.	20 cc. 5/m urea +80 cc. H_2	20 cc. 5/m urea +10 cc. m/1 NaCl +70 cc. H_2O	20 cc. 5/m urea +25 cc. m/1 NaCl +55 cc. H_2O	20 cc. 5/m urea +50 cc. m/1 NaCl +30 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.			
5.15	2.53	3.05	3.50	3.32
20.15	6.54	7.65	9.02	8.93
29.15	7.73	9.03	10.80	10.52
43.15	11.03	12.64	14.54	14.91
52.00	12.85	13.87	17.41	17.75

TABLE XLV

GELATIN—*Urea+Dextrose*

Dry weight of gelatin disc.	0.812	0.812	0.812	0.812	0.814
Solution.	20 cc. 5/m urea +80 cc. H_2O	20 cc 5/m urea + 5 cc. 2/m dextrose +75 cc. H_2O	20 cc. 5/m urea +10 cc. 2/m dextrose +70 cc. H_2O	20 cc. 5/m urea +25 cc. 2/m dextrose +55 cc. H_2O	20 cc. 5/m urea +50 cc. 2/m dextrose +30 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.				
20.30	9.15	9.01	8.56	7.10	5.88
25.30	10.52	10.29	9.78	8.18	6.81
40.30	14.73	14.66	13.87	11.89	10.17
50.00	16.27	16.25	15.49	13.38	11.65

swelling of gelatin in a pyridin solution are shown in Fig. 38 and Table XLIV. The slightly better effects of an osmotically equivalent non-electrolyte (dextrose) are shown in Fig. 39 and Table XLVII.

That the hydrating effects of an amin are largely due to the pure alkali formed on dissociation of the amin in water is proved by such a series of observations as shown in Table XLVIII in which hydrochloric acid is added to an ethylamin solution. As shown in the columns marked II and III, the addition of the acid produces a marked inhibition of the swelling as seen in the pure amin solution. If, however, an amount of acid is added beyond that necessary for neutralization the hydrating effects of the pure

acid become apparent, as shown in the columns marked IV, V, VI, VII and VIII.

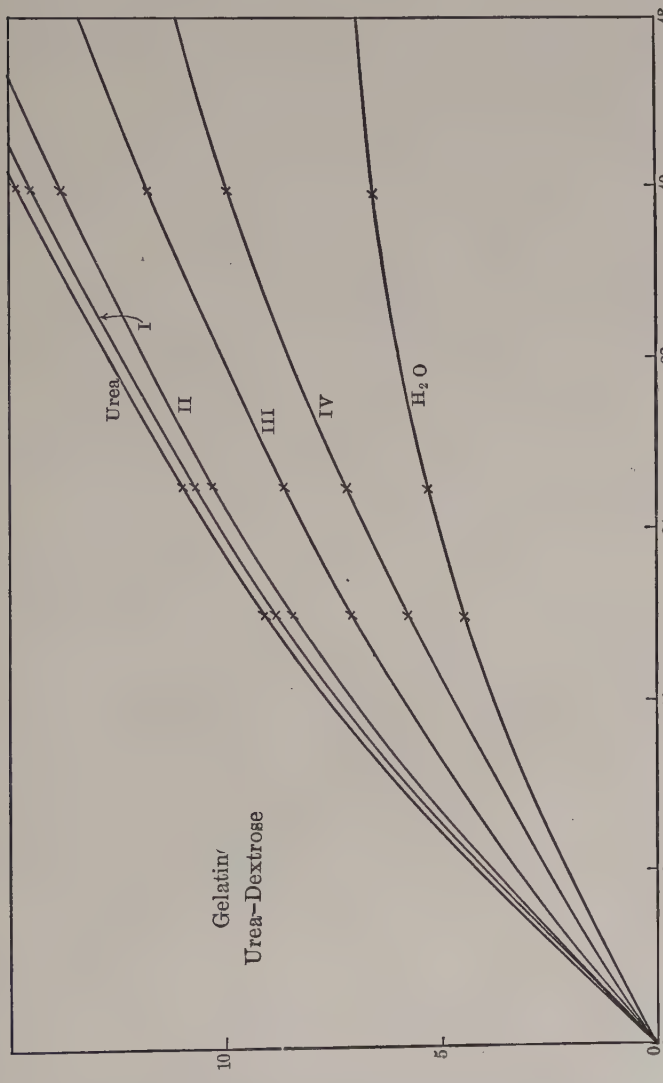


FIGURE 37.

The reducing effects of an electrolyte like sodium chlorid upon the hydration produced in gelatin through ethylamin is illustrated in Fig. 40 and Table XLIX. The ethylamin has, however,

an action due to something besides the effects of the pure alkali formed upon dissociation for Fig. 41 and Table L show the non-

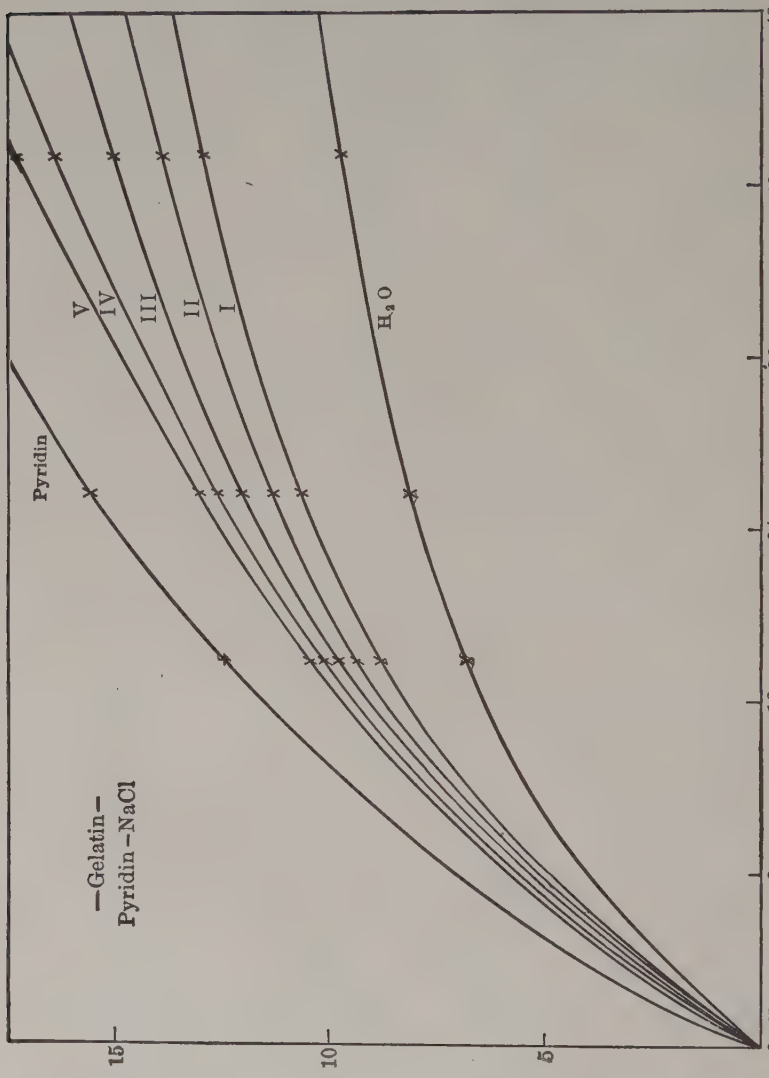


FIGURE 38.

electrolyte used, namely, dextrose, to have an effect larger than anticipated.

It is well in concluding this section to say a word regarding

TABLE XLVI

GELATIN—*Pyridin+NaCl*

Dry weight of gelatin disc.	0.793	0.795	0.812	0.812	0.812	0.816	0.817
Solution	100 cc. H_2O	5 cc. m/1 +95 cc. H_2O	5 cc. m/1 pyridin +5 cc. m/1 NaCl +90 cc. H_2O	5 cc. m/1 pyridin +10 cc. m/1 NaCl +85 cc. H_2O	5 cc. m/1 pyridin +20 cc. m/1 NaCl +75 cc. H_2O	5 cc. m/1 pyridin +30 cc. m/1 NaCl +65 cc. H_2O	5 cc. m/1 pyridin +50 cc. m/1 NaCl +45 cc. H_2O
Hours in the solution	Gain in parts of one part of gelatin						
18.00	6.92	12.35	9.04	9.55	9.99	10.68	10.17
26.30	8.33	15.84	10.92	11.74	12.31	13.30	13.21
42.00	10.01	20.36	13.35	14.25	15.35	16.85	17.69
51.00	9.72	21.28	13.93	14.81	15.97	17.68	18.78
66.00	10.06	23.25	15.04	15.90	17.37	19.89	21.16
			I	II	III	IV	V

TABLE XLVII

GELATIN—*Pyridin+Dextrose*

Dry weight of gelatin disc.	0.793	0.795	0.792	0.790	0.767	0.736	0.736
Solution.	100 cc. H_2O	5 cc. m/1 pyridin +95 cc. H_2O	5 cc. m/1 pyridin + 5 cc. 2/m dextrose +90 cc. H_2O	5 cc. m/1 pyridin +10 cc. 2/m dextrose +85 cc. H_2O	5 cc. m/1 pyridin +20 cc. 2/m dextrose +75 cc. H_2O	5 cc. m/1 pyridin +30 cc. 2/m dextrose +65 cc. H_2O	5 cc. m/1 pyridin +50 cc. 2/m dextrose +45 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.						
18.00	6.92	12.35	11.60	10.32	9.24	8.79	6.67
26.30	8.33	15.84	14.46	13.12	11.77	10.92	8.29
42.00	10.01	20.36	18.46	16.94	15.09	13.69	10.53
51.00	9.72	21.28	18.85	17.65	15.78	14.32	11.18
66.00	10.06	23.25	17.72	19.28	17.13	15.63	12.62

the *similarities and the differences to be noted between the swelling of fibrin and the swelling of gelatin.* The two behave similarly in that both swell more in the solutions of acids and alkalies than in water; both swell to different degrees in equinormal solutions of different acids or alkalies, and the order in which these acids

and alkalies are effective is much the same; the swelling of both in either acid or alkaline solutions is markedly inhibited through the presence of electrolytes, and this the more the higher the

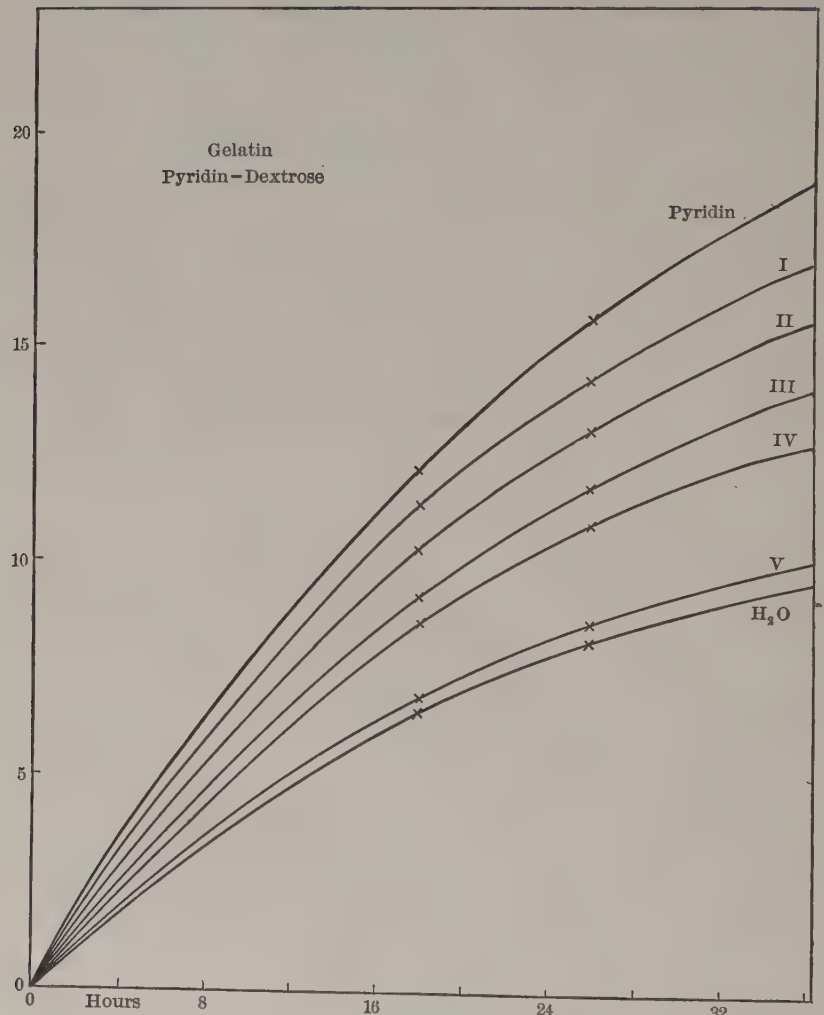


FIGURE 39.

concentration of the electrolytes. In contrast to the action of the electrolytes, the non-electrolytes are comparatively ineffective in this regard.

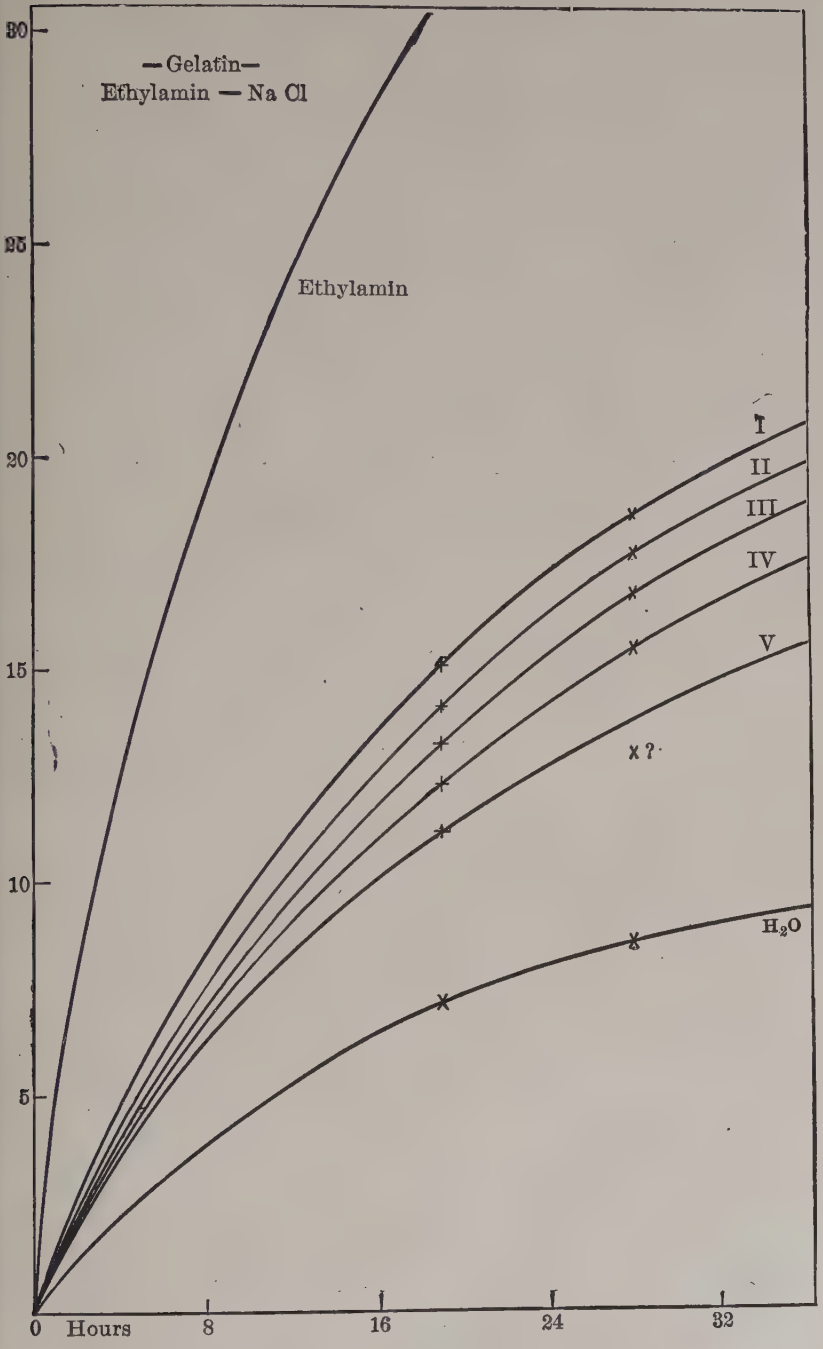

30
25
20
15
10
5
—Gelatin—
Ethylamin — Na Cl
Ethylamin
I
II
III
IV
V
x ?
H_2O
0 Hours
8
16
24
32

FIGURE 40.

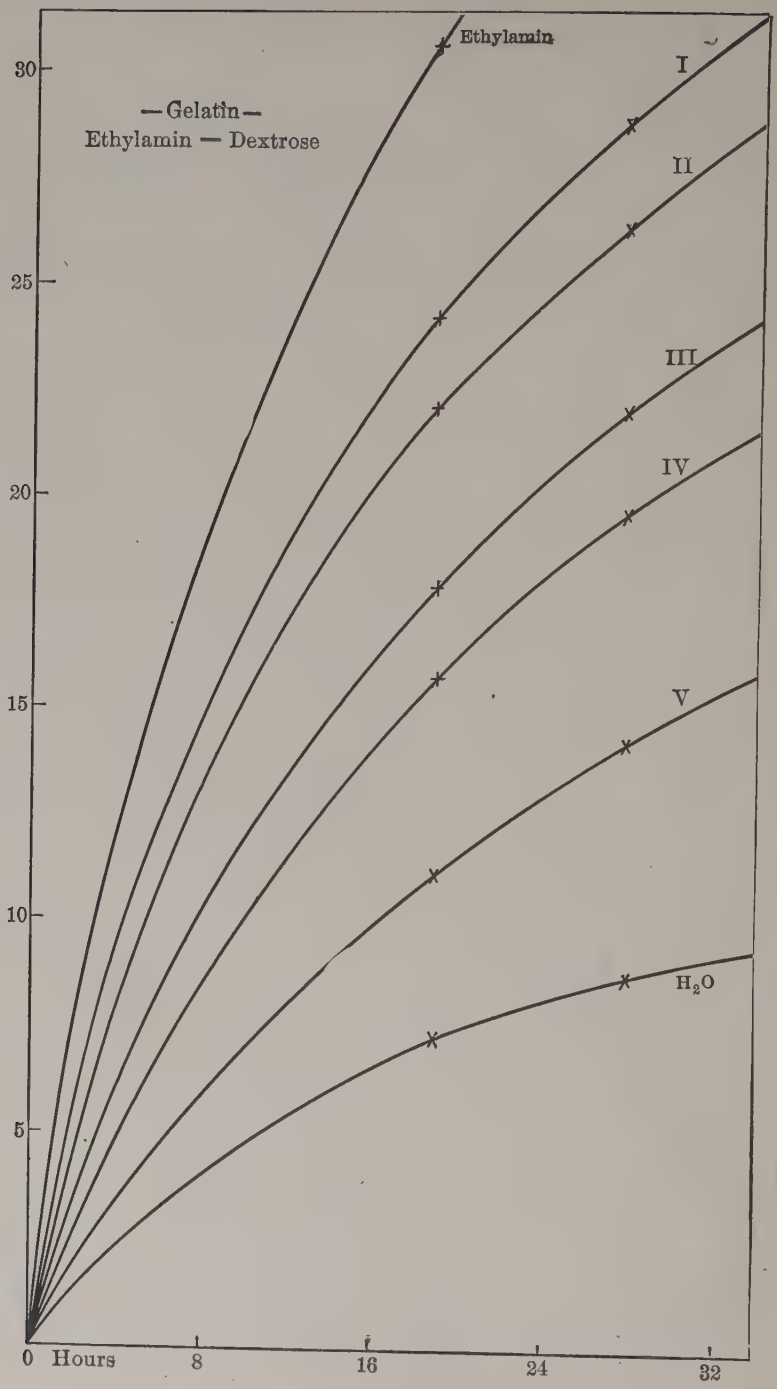

Ethylamin
I
II
III
IV
V
H_2O
—Gelatin—
Ethylamin — Dextrose
30
25
20
15
10
5
0 Hours
8
16
24
32

FIGURE 41.

TABLE XLVIII

GELATIN—*Ethylamin+HCl*

Dry weight of gelatin disc.	0.743	0.744	0.747	0.749	0.750
Solution	100 cc. H_2O	5 cc. m/1 ethylamin +95 cc. H_2O	5 cc. m/1 ethylamin +25 cc. n/10 HCl +70 cc. H_2O	5 cc. m/1 ethylamin +50 cc. n/10 HCl +45 cc. H_2O	5 cc. m/1 ethylamin +60 cc. n/10 HCl +35 cc. H_2O
Hours in the solution	Gain in parts of one part of gelatin				
16.30	4.80	18.30	9.33	8.95	14.85
24.30	5.54	20.85	10.83	10.74	18.98
39.00	6.57	22.84	12.23	13.28	22.72
48.00	6.84	22.60	12.33	13.85	25.17
63.00	8.45	21.93	12.36	14.67	27.05
		I	II	III	IV

Dry weight of gelatin disc.	0.750	0.752	0.753	0.753
Solution	5 cc. m/1 ethylamin +70 cc. n/10 HCl +25 cc. H_2O	5 cc. m/1 ethylamin +80 cc. n/10 HCl +15 cc. H_2O	5 cc. m/1 ethylamin +90 cc. n/10 HCl +5 cc. H_2O	1 cc. 5/m ethylamin +99 cc. n/10 HCl
Hours in the solution	Gain in parts of one part of gelatin			
16.30	16.73	16.73	15.87	15.00
24.30	20.64	20.76	19.62	18.07
39.00	26.88	27.05	24.71	23.80
48.00	29.26	29.22	27.46	25.70
63.00	33.06	33.50	33.36	30.75
	V	VI	VII	VIII

Urea and pyridin are representative of another class of substances which increase the power of both fibrin and gelatin to swell, but this type of increased hydration, while not affected by salts is markedly reduced through various non-electrolytes such as the sugars.

There exist, on the other hand, certain differences between the swelling of fibrin and the swelling of gelatin. These are for the most part of a quantitative nature. Gelatin is able to absorb under optimal conditions about sixty-five times its weight in water. With fibrin I have obtained values up to forty times its weight in absorbed water. While fibrin swells more in alkaline

TABLE XLIX

GELATIN—*Ethylamin+NaCl*

Dry weight of gelatin disc.	0.725	0.726	0.726	0.727	0.728	0.728	0.728
Solution	100 cc. H_2O	5 cc. m/1 ethylamin +95 cc. H_2O	5 cc. m/1 ethylamin +5 cc. m/1 NaCl +90 cc. H_2O	5 cc. m/1 ethylamin +10 cc. m/1 NaCl +85 cc. H_2O	5 cc. m/1 ethylamin +20 cc. m/1 NaCl +75 cc. H_2O	5 cc. m/1 ethylamin +30 cc. m/1 NaCl +65 cc. H_2O	5 cc. m/1 ethylamin +50 cc. m/1 NaCl +45 cc. H_2O
Hours in the solution	Gain in parts of one part of gelatin						
19.00	7.49	30.85	15.10	14.29	13.33	12.50	10.54
27.30	8.71	36.02	17.92	16.97	15.87	15.28	13.18
43.30	10.16	38.55	22.18	21.52	20.55	18.47	16.97
51.00	10.69	38.28	24.08	23.19	22.61	20.82	19.02
66.00	12.38	37.58	26.91	25.18	24.76	22.61	Complete solution
			I	II	III	IV	V

TABLE L

GELATIN—*Ethylamin+Dextrose*

Dry weight of gelatin disc.	0.725	0.726	0.732	0.732	0.733	0.734	0.735
Solution	100 cc. H_2O	5 cc. m/1 ethylamin +95 cc. H_2O	5 cc. m/1 ethylamin +5 cc. 2/m dextrose +90 cc. H_2O	5 cc. m/1 ethylamin +10 cc. 2/m dextrose +85 cc. H_2O	5 cc. m/1 ethylamin +20 cc. 2/m dextrose +75 cc. H_2O	5 cc. m/1 ethylamin +30 cc. 2/m dextrose +65 cc. H_2O	5 cc. m/1 ethylamin +50 cc. 2/m dextrose +45 cc. H_2O
Hours in the solution	Gain in parts of one part of gelatin						
19.00	7.49	30.85	24.62	22.34	18.26	16.27	11.42
27.30	8.71	36.02	28.91	26.39	22.22	20.09	14.24
43.30	10.16	38.55	33.25	30.78	26.46	23.70	17.70
51.00	10.69	38.25	33.37	30.99	26.54	24.80	17.92
66.00	12.38	37.58	34.97	32.25	28.60	26.26	19.72

solutions than in equally concentrated acid solutions, gelatin does the reverse. This may, however, be only a seeming difference, because of the usual acid content of the commercial gelatins, and the consequent formation of salts when they are made to swell in alkaline solutions. Fibrin attains its maximal swelling in concentrations of acid which are much below those necessary to pro-

duce the maximum amount of swelling in gelatin, and higher concentrations of electrolytes are necessary to reduce markedly the swelling of gelatin in acid solutions than are necessary in the case of fibrin. On the other hand, urea and pyridin seem able to induce a relatively higher hydration in gelatin than in fibrin. All these statements must, however, not be taken too strictly, for depending upon the history of their preparation, etc., the gelatins differ widely from each other.

Such similarities and differences in the behavior of different colloids toward the same external conditions demand detailed study, for they are of the utmost biological importance. Protoplasm consists of a mixture of many different colloids. Not only are different colloids found in the same cell, but essentially different colloids form the basis of different tissues (bone, cartilage, muscle, connective tissue, parenchymatous organs, central nervous system). It is at once apparent, therefore, that not only so far as water absorption and secretion is concerned, but so far as any physiological reaction dependent upon the colloid constitution of living matter is concerned, a single variation in internal or external conditions may be followed by quite a different response either qualitatively or quantitatively, not only by different tissues, but by different parts of the same tissue or even the same cell. In a study of the behavior of different colloids toward the same group of external conditions we may therefore hope to discover much to aid us in our attempt to analyze the apparently limitless variations in the reactions of protoplasm to various external " stimuli."

4. Observations on the Swelling of Gluten.

The absorption of water by proteins has recently received interesting elaboration by the work of Fred W. Upson and J. W. Calvin [1] in their study of wheat gluten. The gluten was prepared by washing flour free of its starch with distilled water. It was rolled out between glass plates to uniform thickness, and small round pellets weighing approximately 1.25 gram were cut from this with a large cork borer. Gluten behaves very much like fibrin and gelatin. Thus, it swells more in any acid than

[1] Fred W. Upson and J. W. Calvin: Personal Communication (1914); Jour. Am. Chem. Soc., 37, 1295 (1915).

in pure water. This is well shown in Fig. 42. The beaker on the extreme left shows a pellet of gluten in distilled water. The six beakers to the right contain progressively stronger solutions

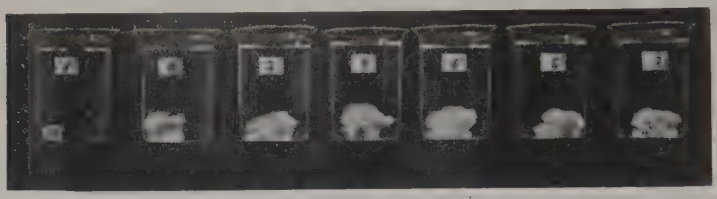


FIGURE 42.

of lactic acid ranging from n/500 to n/10. Entirely similar series may be arranged for other acids.

FIGURE 43.

The addition of any salt to an acid solution inhibits the swelling, and this the more the higher the concentration of the added salt. This is well illustrated in Figs. 43, 44 and 45. Beaker 1

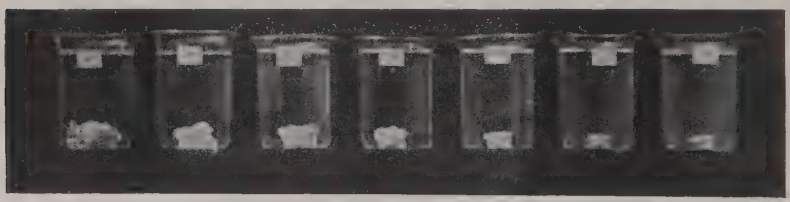


FIGURE 44.

in each of the series contains pure n/100 lactic acid; the remaining beakers, increasingly greater amounts (from m/1000 to m/25) of different salts, potassium chlorid in Fig. 43, dipotassium phosphate in Fig. 44 and potassium tartrate in Fig. 45.

Figs. 46 and 47 bring out these relationships yet more clearly.

In Fig. 47 is shown the amount of water absorbed in different concentrations of three different acids. Concentration is plotted

FIGURE 45.

on the horizontal, increase in weight in terms of the original weight of the (moist) pellet on the vertical. The optimal swelling point is exceeded earlier in the case of hydrochloric acid than

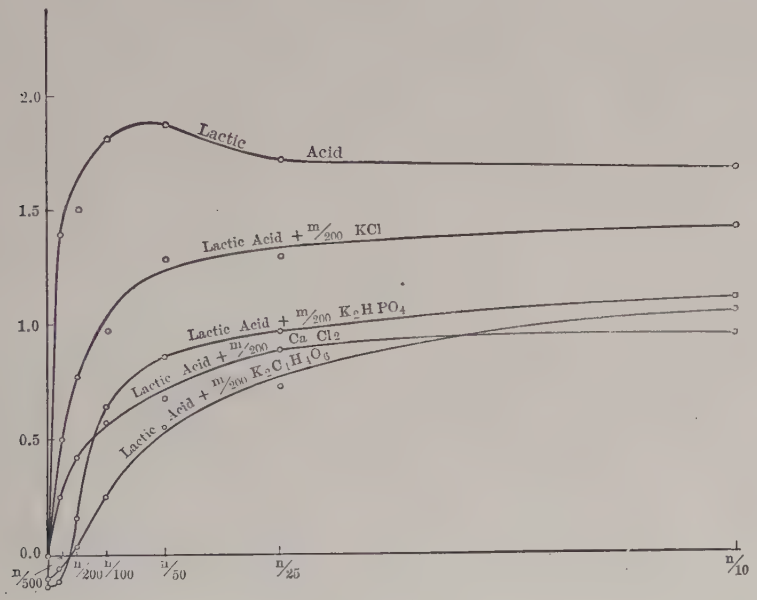


FIGURE 46.

in the case of lactic or acetic. A highly interesting feature of these gluten experiments is the fact that even such "weak" acids as lactic and acetic show an optimal concentration for swelling beyond which the protein swells less than in lower concentrations of the acid.

Acetic Acid
Lactic Acid
Hydrochloric Acid
2.0
1.5
1.0
0.5
0.0
n/200
n/100
n/50
n/25
n/10
n/5
n/2

FIGURE 47.

Fig. 46, in addition to showing that all salts reduce the swelling of gluten in an acid solution, also shows that at the same concentration different salts are unequally effective in this regard. Thus, calcium chlorid produces a greater dehydration than potassium chlorid, and the tartrate is more powerful than the phosphate.

Some earlier experiments by T. B. Wood and W. B. Hardy [1] on the "cohesiveness" of gluten bring out from an experimental point of view what amount in essence to the same facts as those of Upson and Calvin. Wood and Hardy found gluten to "disintegrate" and "dissolve" in dilute acids. The loss of cohesion depended upon the nature of the acid and its concentration and in about the way in which the swelling of fibrin, gelatin and gluten depends upon these factors. Salts inhibited the action of the acid, both their concentration and their nature being of great importance in the matter.

These experiments show how plant protein behaves in a fashion identical with the previously studied animal proteins. Their importance in the general biological problem of water absorption will become apparent as we proceed. The value of Wood, Hardy, Upson and Calvin's work in many other directions, as for the theory and practice of flour manufacture, bread making, etc., needs no emphasis.[2]

5. Observations on the Swelling of Aleuronat

In order to obtain data upon the water-absorbing powers of another plant protein, the behavior of "natural" aleuronat grains was studied.[3] Aleuronat, as is well known, is not a single protein but a mixture of several. The results detailed in the following

[1] T. B. Wood and W. B. Hardy: Proc. Roy. Soc., London, Series B, **81**, 38 (1908).

[2] See in this connection F. W. Upson and J. W. Calvin: Bull. Agric. Exp. Station of Nebraska, Research Bull. No. 8 (1916); also Wolfgang Ostwald: Kolloid-Zeitschr., **25**, 26 (1919); H. Luers and Wolfgang Ostwald: ibid., **25**, 82 (1919). See also L. J. Henderson and E. J. Cohn: Jour. Biol. Chem., **36**, 581 (1918); L. J. Henderson: Jour. General Physiology, **1**, 387 (1919); ibid., **1**, 459 (1919). In these papers Cohn and Henderson accept as correct for the swelling of flour proteins all the laws, previously stated by me for the swelling of animal proteins in health and disease and the correctness of which they have so often denied.

[3] Martin H. Fischer and Marian O. Hooker: Kolloid-Zeitschr., **26**, 49 (1920); these studies were ready for publication in 1916 since which time they were held by the British censor.

experiments are in consequence not to be interpreted as the effects of various external conditions upon a single protein, but rather as the sum of such effects upon several. Since living cells, however, also contain several proteins in mixture, the behavior of aleuronat is of significance for the analysis of living cells when subjected to similar conditions.

The experiments were carried out by introducing weighed amounts (one gram) of air dry aleuronat into calibrated test tubes (19 mm. in diameter) containing a constant volume of liquid (40 cc.). The degree of swelling of the aleuronat was then expressed by measuring the height of the aleuronat columns in the different tubes. After introducing the aleuronat into the different solutions the contents of the tubes were thoroughly mixed by turning these about several times, care being taken to treat all in exactly the same fashion. Like most colloid reactions, the swelling of aleuronat takes time. Unless otherwise specified, measurements as given below refer to the values obtained in the different media at the end of eighteen hours.

(*a*) Excepting in very low concentrations of acid, aleuronat swells more in such a medium than in distilled water. This is shown in Table LI. The figures in the columns should be read downwards as this is the order in which each series of experiments was done. With slight allowance for errors, due to uneven settling, etc., the columns may also, however, be read across.

Table LI shows that in the case of the "strong" acids (hydro-

TABLE LI

ALEURONAT—*Acids*

Concentration of solution	Height of aleuronat column in mm. after 18 hours in					
	Hydrochloric	Nitric	Sulphuric	Lactic	Formic	Tartaric
40 cc. H_2O (control)	24	25	25	25	25	25
1 cc. n/10 acid +39 cc. H_2O	22	23	23	24	22	23
2 cc. " " +38 cc. "	37	23	24	34	31	25
3 cc. " " +37 cc. "	44	40	26	38	37	29
4 cc. " " +36 cc. "	**49**	**42**	26	41	38	33
5 cc. " " +35 cc. "	48	39	**26**	44	39	35
7½ cc. " " +32½ cc. "	45	34	25	47	43	40
10 cc. " " +30 cc. "	40	29	25	48	45	44
15 cc. " " +25 cc. "	34	25	25	49	45	46
20 cc. " " +20 cc. "	31	25	26	53	47	48
30 cc. " " +10 cc. "	28	25	26	55	50	50
40 cc. n/10 acid	27	25	26	**55**	**50**	**50**

chloric, nitric, sulphuric) there is with every increase in concentration an increase in swelling, but this continues only up to a certain point beyond which a decreased swelling is noted. Figs.

FIGURE 48.

48 and 49, in which are reproduced photographically the results for hydrochloric and sulphuric acids, illustrate this behavior better than many words. In the case of the "weak" acids (lactic, formic, tartaric) there is, with progressive increase in concentration, within the limits used in these experiments, only a pro-

gressive increase in swelling. Fig. 50 shows the appearance of the tubes when lactic acid is used.

Table LI reaffirms the older findings which, while often emphasized before, have not as yet received adequate consideration at the hands of critics who, in working on the problems of acid intoxication in living organisms, remain ignorant of these simple facts regarding the effects of acids upon ordinary proteins. The table again shows that the degree of swelling is nowhere proportional to the hydrogen ion concentration alone. Sulphuric acid, for

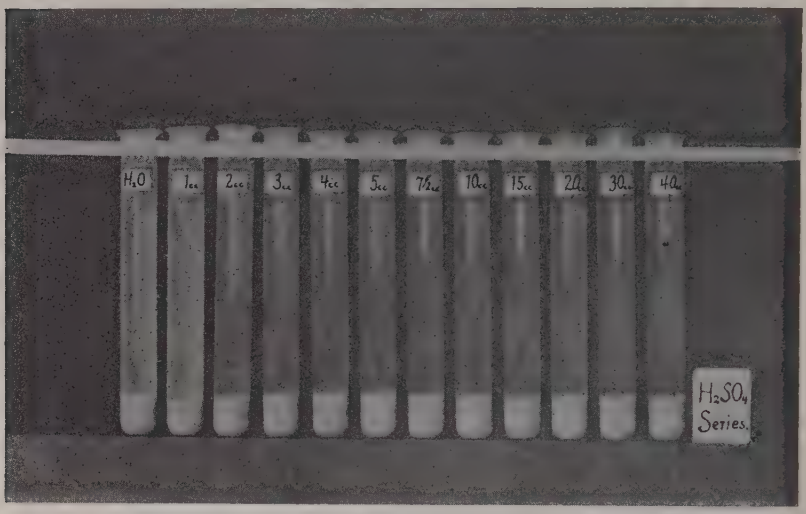


FIGURE 49.

example, which in these dilute solutions yields, on dissociation, about the same number of hydrogen ions as nitric or hydrochloric acid produces little more swelling than distilled water. On the other hand, the weakly dissociated lactic, formic and tartaric acids are, in the production of swelling almost as powerful as hydrochloric. As the end members of these series show, there exist concentrations of such "weak" organic acids capable of producing an even greater swelling of aleuronat than is produced by the optimal concentrations of hydrochloric or nitric acids.

Table LI shows that in the lowermost acid concentration there is even less swelling of the aleuronat than in pure water. This

effect of very low concentrations of acid in producing a slight decrease in the swelling of aleuronat is brought out in greater detail in Table LII.

TABLE LII

ALEURONAT—*Acids*

Concentration of solution	Height of aleuronat column in mm. after 18 hours in	
	Hydrochloric	Nitric
40 cc. H_2O (control)	24	24
0.1 cc. n/10 acid +39.9 cc. H_2O	24	24
0.2 cc. " " +39.8 cc. "	23	24
0.3 cc. " " +39.7 cc. "	**22**	24
0.4 cc. " " +39.6 cc. "	23	24
0.5 cc. " " +39.5 cc. "	23	24
0.75 cc. " " +39.25 cc. "	23	22
1. cc. " " +39. cc. "	23	**21**
2. cc. " " +38. cc. "	36	30
3. cc. " " +37. cc. "	42	35
4. cc. " " +36. cc. "	46	38
5. cc. " " +35. cc. "	46	38

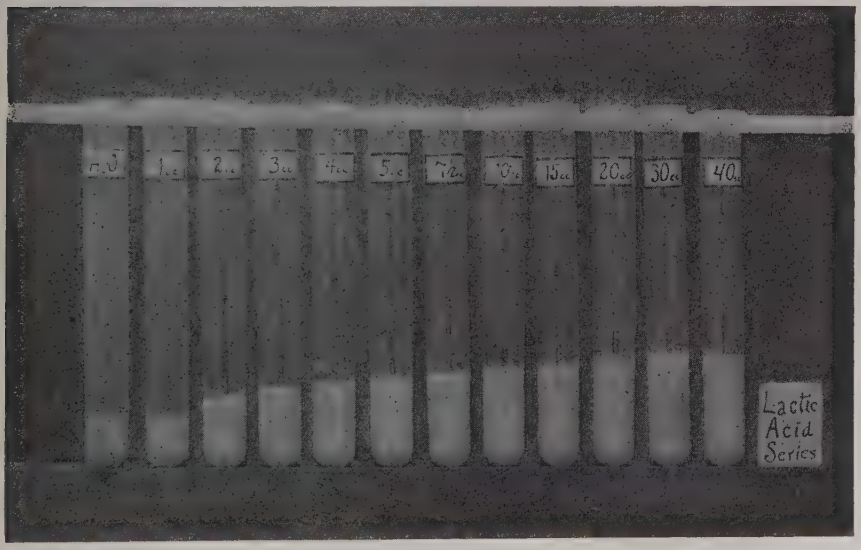


FIGURE 50.

(*b*) The swelling of aleuronat is greater in alkalies than in pure water. This is illustrated for sodium hydroxid in Table LIII and

Fig. 51. The amount of swelling at first rises with progressive increase in the concentration of the alkali until an optimum is

TABLE LIII

ALEURONAT—*Sodium Hydroxid*

Concentration of solution	Height of aleuronat column in mm. after 18 hours
40 cc. H_2O (control)	24
1 cc. n/10 NaOH +39 cc. H_2O	22
2 cc. " " +38 cc. "	32
3 cc. " " +37 cc. "	32
4 cc. " " +36 cc. "	34
5 cc. " " +35 cc. "	36
7.5 cc. " " +32.5 cc. "	**41**
10 cc. " " +30 cc. "	38
15 cc. " " +25 cc. "	33
20 cc. " " +20 cc. "	30
30 cc. " " +10 cc. "	25
40 cc. n/10 NaOH	23

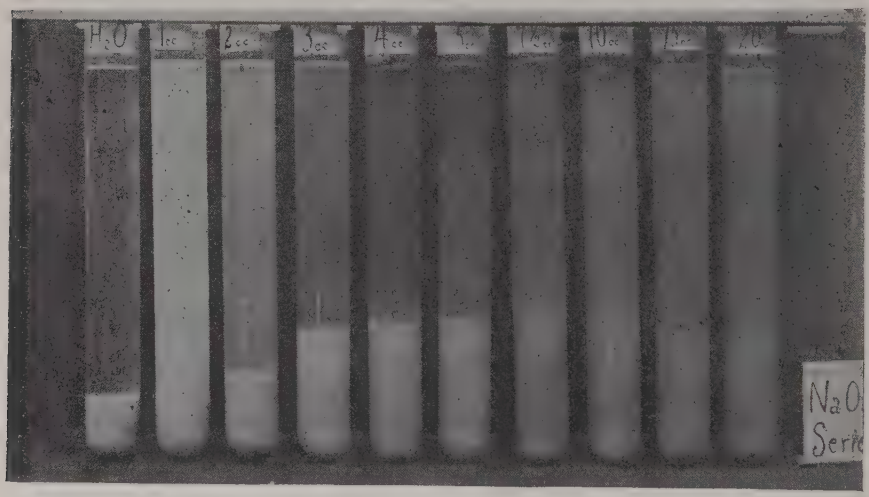


FIGURE 51.

reached, beyond which further addition of alkali brings about a diminished swelling. In very low concentrations of alkali the amount of swelling may actually be slightly less than in pure water, as apparent in the second tube from the left in Fig. 51 and as illustrated in greater detail in Table LIV.

(*c*) As previously noted for other proteins, the addition of

TABLE LIV

ALEURONAT—*Sodium Hydroxid*

Concentration of solution	Height of aleuronat column in mm. after 18 hours
40 cc. H_2O (control)	24
0.1 cc. n/10 NaOH +39.9 cc. H_2O	25
0.2 cc. " " +39.8 cc. "	25
0.3 cc. " " +39.7 cc. "	25
0.4 cc. " " +39.6 cc. "	24
0.5 cc. " " +39.5 cc. "	24
0.6 cc. " " +39.4 cc. "	24
0.8 cc. " " +39.2 cc. "	23
1.0 cc. " " +39.0 cc. "	23
1.5 cc. " " +38.5 cc. "	26
2.0 cc. " " +38.0 cc. "	32
3.0 cc. " " +37.0 cc. "	40

various salts reduces the amount of swelling induced in aleuronat by any acid or alkali. Table LV and Fig. 52 reproduce the findings obtained when sodium chlorid is added in increasing concentration to hydrochloric acid, while Tables LVI and LVII with the corresponding Figs. 53 and 54 show the results when sodium chlorid and sodium sulphate are added, respectively, to sodium hydroxid. In all instances there is a progressive decrease in amount of swelling as the concentration of the added salt rises.

TABLE LV

ALEURONAT—*Acid+Sodium Chlorid*

Concentration of solution	Height of aleuronat column in mm. after 18 hours
40 cc. H_2O (control)	24
5 cc. n/10 HCl +36.0 cc. H_2O	44
5 cc. n/10 HCl +0.1 cc. m/1 NaCl +35.9 cc. H_2O	38
5 cc. " " +0.2 cc. " " +35.8 cc "	37
5 cc. " " +0.3 cc. " " +35.7 cc. "	34
5 cc. " " +0.4 cc. " " +35.6 cc. "	32
5 cc. " " +0.5 cc. " " +35.5 cc. "	31
5 cc. " " +0.75 cc. " " +35.25 cc. "	29
5 cc. " " +1.0 cc. " " +35.0 cc. "	27
5 cc. " " +1.25 cc. " " +34.75 cc. "	26
5 cc. " " +1.5 cc. " " +34.5 cc. "	28
5 cc. " " +2.0 cc. " " +34.0 cc. "	28

(*d*) While all salts decrease the swelling of aleuronat in the presence of an acid or an alkali certain salts are more powerful in this regard than are others. The comparative effects of a series of potassium salts upon swelling in hydrochloric acid are shown in

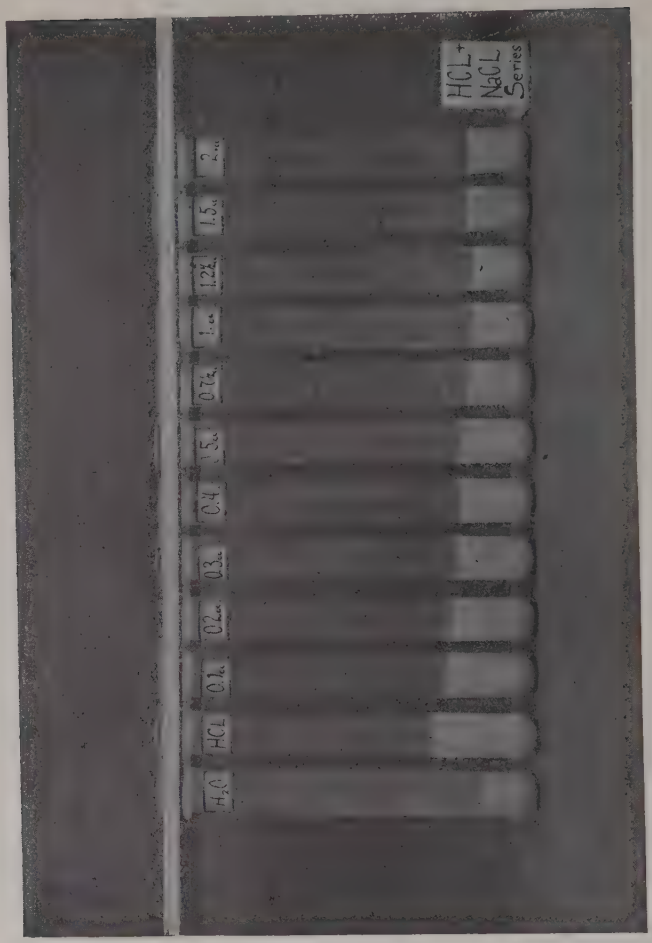


FIGURE 52.

TABLE LVI

ALEURONAT—*Alkali+Sodium Chlorid*

Concentration of solution	Height of aleuronat column in mm. after 18 hours
40 cc. H_2O (control)	25
5 cc. n/10 NaOH +36 cc. H_2O	36
5 cc. n/10 NaOH +0.1 cc. m/1 NaCl +35.9 cc. H_2O	35
5 cc. " " +0.2 cc. " " +35.8 cc. "	35
5 cc. " " +0.3 cc. " " +35.7 cc. "	34
5 cc. " " +0.4 cc. " " +35.6 cc. "	34
5 cc. " " +0.5 cc. " " +35.5 cc. "	34
5 cc. " " +0.75 cc. " " +35.25 cc. "	35
5 cc. " " +1.0 cc. " " +35.0 cc. "	34
5 cc. " " +1.25 cc. " " +34.75 cc. "	33
5 cc. " " +1.5 cc. " " +34.5 cc. "	34
5 cc. " " +2.0 cc. " " +34.0 cc. "	33

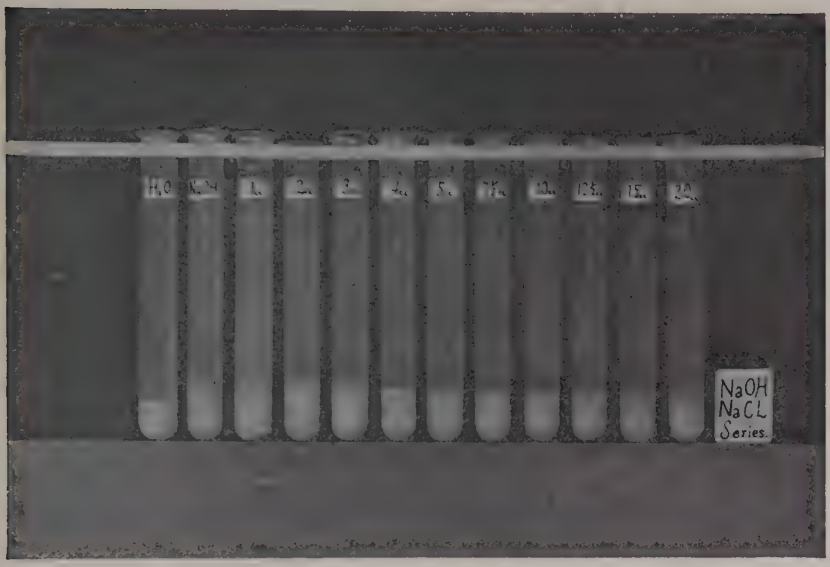


FIGURE 53.

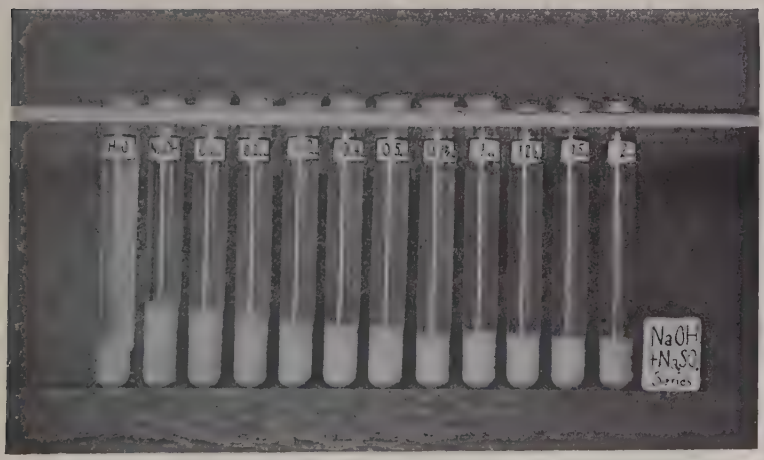


FIGURE 54.

Table LVIII and Fig. 55; the effects of the same series upon swelling in sodium hydroxid are shown in Table LIX. While in the first instance the order, when that least powerful is given first, is: chlorid, bromid, nitrate, iodid, acetate, sulpho-

TABLE LVII

ALEURONAT—*Alkali+Sodium Sulphate*

Concentration of solution	Height of aleuronat column in mm. after 18 hours
40 cc. H_2O (control)	25
4 cc. n/10 NaOH +36 cc. H_2O	42
4 cc. n/10 NaOH +0.1 cc. m/1 Na_2SO_4 +35.9 cc. H_2O	38
4 cc. " " +0.2 cc. " " +35.8 cc. "	36
4 cc. " " +0.3 cc. " " +35.7 cc. "	35
4 cc. " " +0.4 cc. " " +35.6 cc. "	33
4 cc. " " +0.5 cc. " " +35.5 cc. "	32
4 cc. " " +0.75 cc. " " +35.25 cc. "	29
4 cc. " " +1.0 cc. " " +35.0 cc. "	29
4 cc. " " +1.25 cc. " " +34.75 cc. "	28
4 cc. " " +1.5 cc. " " +34.5 cc. "	28
4 cc. " " +2.0 cc. " " +34.0 cc. "	27

TABLE LVIII

ALEURONAT—*Acid+Potassium Salts*

Concentration of solution	Height of aleuronat column in mm. after 18 hours
40 cc. H_2O (control)	25
4 cc. n/10 HCl +36 cc. H_2O	51
4 cc. n/10 HCl +0.1 cc. m/1 K chlorid +35.9 cc. H_2O	46
4 cc. " " +0.1 cc. " K bromid +35.9 cc. "	46
4 cc. " " +0.1 cc. " K nitrate +35.9 cc. "	45
4 cc. " " +0.1 cc. " K iodid +35.9 cc. "	43
4 cc. " " +0.1 cc. " K acetate +35.9 cc. "	42
4 cc. " " +0.1 cc. " K sulphocyanate +35.9 cc. "	41
4 cc. " " +0.1 cc. " K tartrate +35.9 cc. "	38
4 cc. " " +0.1 cc. " K citrate +35.9 cc. "	23

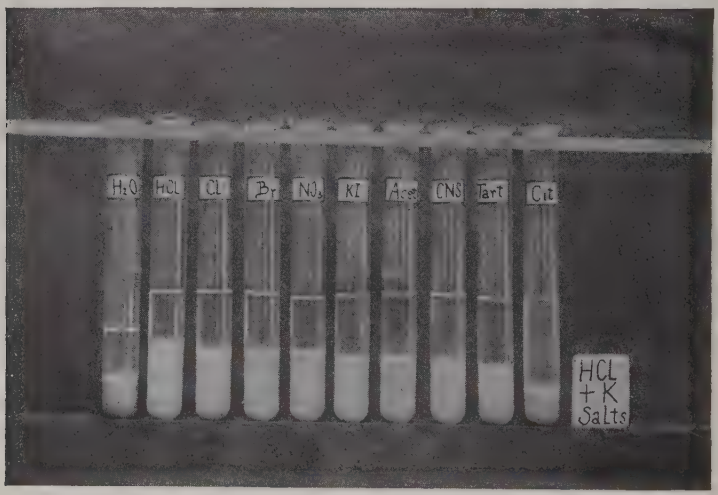


FIGURE 55.

cyanate, tartrate, citrate, this order is practically reversed in the second.

TABLE LIX

ALEURONAT—*Alkali+Potassium Salts*

Concentration of solution	Height of aleuronat column in mm. after 18 hours
40 cc. H_2O (control)	25
4 cc. n/10 NaOH+36 cc. H_2O	37
4 cc. n/10 NaOH+0.1 cc. m/1 K citrate +35.9 cc. H_2O	36
4 cc. " " +0.1 cc. " K tartrate +35.9 cc. "	36
4 cc. " " +0.1 cc. " K acetate +35.9 cc. "	35
4 cc. " " +0.1 cc. " K bromid +35.9 cc. "	35
4 cc. " " +0.1 cc. " K nitrate +35.9 cc. "	34
4 cc. " " +0.1 cc. " K sulphocyanate +35.9 cc. "	34
4 cc. " " +0.1 cc. " K iodid +35.9 cc. "	31
4 cc. " " +0.1 cc. " K chlorid +35.9 cc. "	31

TABLE LX

ALEURONAT—*Acid+Chlorids*

Concentration of solution	Height of aleuronat column in mm. after 18 hours
40 cc. H_2O (control)	24
4 cc. n/10 HCl+36 cc. H_2O	53
4 cc. n/10 HCl+0.1 cc. m/1 iron (ic) +35.9 cc. H_2O	57
4 cc. " " +0.1 cc. " aluminium +35.9 cc. "	52
4 cc. " " +0.1 cc. " ammonium +35.9 cc. "	49
4 cc. " " +0.1 cc. " sodium +35.9 cc. "	47
4 cc. " " +0.1 cc. " copper (ic) +35.9 cc. "	47
4 cc. " " +0.1 cc. " magnesium +35.9 cc. "	46
4 cc. " " +0.1 cc. " calcium +35.9 cc. "	45
4 cc. " " +0.1 cc. " strontium +35.9 cc. "	44

TABLE LXI

ALEURONAT—*Alkali+Chlorids*

Concentration of solution	Height of aleuronat column in mm. after 18 hours
40 cc. H_2O (control)	25
4 cc. n/10 NaOH	37
4 cc. n/10 NaOH+0.1 cc. m/1 NaCl +35.9 cc. H_2O	36
4 cc. " " +0.1 cc. " NH_4Cl +35.9 cc. "	35
4 cc. " " +0.1 cc. " $FeCl_3$ +35.9 cc. "	33
4 cc. " " +0.1 cc. " $SrCl_2$ +35.9 cc. "	32
4 cc. " " +0.1 cc. " $CaCl_2$ +35.9 cc. "	29
4 cc. " " +0.1 cc. " $MgCl_2$ +35.9 cc. "	27
4 cc. " " +0.1 cc. " $AlCl_3$ +35.9 cc. "	27
4 cc. " " +0.1 cc. " $CuCl_2$ +35.9 cc. "	26

The effects of salts with a common acid radical but different basic ones in reducing, at a given concentration, the swelling of aleuronat in the presence of an acid or an alkali are shown in Tables LX and LXI. All these salts reduce swelling with the exception of those in the acid series which hydrolyze strongly and thus tend to yield an overplus of acid. The order in

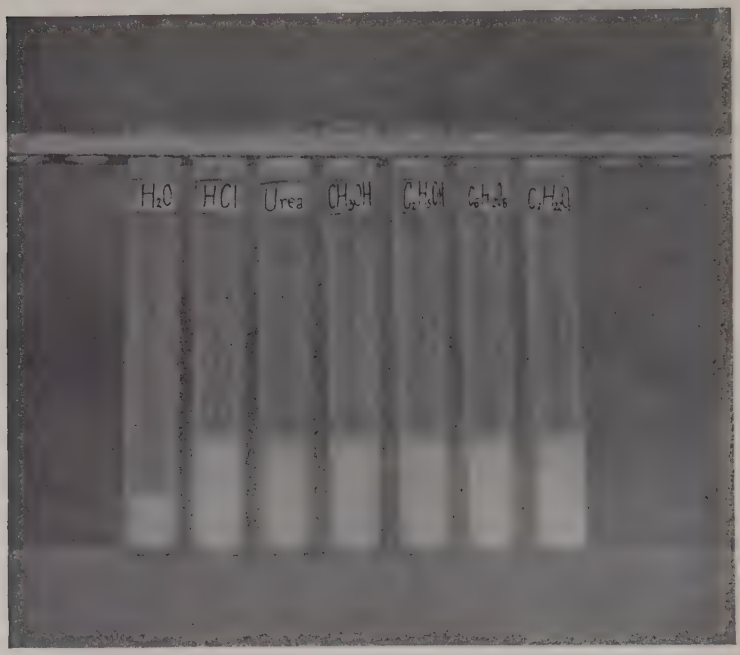


FIGURE 56.

which the different basic radicals prove effective may be seen in the tables.

(*e*) At an "osmotic" concentration about equal to that in which the different salts greatly reduce the swelling of aleuronat in the presence of an acid or alkali, different non-electrolytes are practically without effect. Tables LXII and LXIII and Fig. 56 illustrating the acid series show this. The swelling in the presence of urea, or the two alcohols or the two sugars is not measurably different from that in the pure acid.

TABLE LXII

ALEURONAT—*Acid+Non-Electrolytes*

Concentration of solution	Height of aleuronat column in mm. after 18 hours
40 cc. H_2O (control)	25
4 cc. n/10 HCl+36 cc. H_2O	48
4 cc. n/10 HCl+0.1 cc. 2 m. urea +35.9 cc. H_2O	48
4 cc. " " +0.1 cc. " methyl alcohol +35.9 cc. "	48
4 cc. " " +0.1 cc. " ethyl alcohol +35.9 cc. "	48
4 cc. " " +0.1 cc. " dextrose +35.9 cc. "	49
4 cc. " " +0.1 cc. " saccharose +35.9 cc. "	49

TABLE LXIII

ALEURONAT—*Alkali+Non-Electrolytes*

Concentration of solution	Height of aleuronat column in mm. after 18 hours
40 cc. H_2O (control)	25
4 cc. n/10 NaOH+36 cc. H_2O	38
4 cc. n/10 NaOH+0.1 cc. 2 m. urea +35.9 cc. H_2O	38
4 cc. " " +0.1 cc. " methyl alcohol +35.9 cc. "	38
4 cc. " " +0.1 cc. " ethyl alcohol +35.9 cc. "	38
4 cc. " " +0.1 cc. " dextrose +35.9 cc. "	36
4 cc. " " +0.1 cc. " saccharose +35.9 cc. "	38

6. Hydration and Dehydration in Liquid Colloids

The three colloids discussed thus far are essentially solid in character, and their behavior corresponds, as we shall see immediately, with the more solid constituents of living matter such as the muscles, parenchymatous organs, nervous tissues or eyes of our own bodies. But permeating these more solid structures we find in the higher animals streams of liquid colloid material which we call blood, lymph or tissue juice. How do such liquid protein colloids behave when subjected to the action of acids, alkalies and salts? Do they "swell" and "shrink" as do the solid colloids already discussed? The answer to this question, which is of fundamental importance for the solution of a whole series of biological phenomena, has been given us through the work, more especially of FRANZ HOFMEISTER,[1], WOLFGANG

[1] FRANZ HOFMEISTER: Arch. f. exp. Path. u. Pharm., **27**, 395 (1890); ibid., **28**, 210 (1891).

Pauli,[1] W. B. Hardy,[2] P. von Schroeder,[3] Hans Handovsky[4] and K. Schorr.[5] A liquid colloid such as a solution of gelatin, blood serum or egg albumin cannot, of course, be seen to swell or shrink in a test-tube. We must therefore use some other method of discovering such changes and measuring them. This is accomplished by determining the viscosity of the liquid colloid by permitting it to flow through a capillary tube. Evidently, as the separate colloid particles in a colloid solution swell, they take up the pure solvent about them, and as such swelling progresses it must become increasingly difficult for the particles to move over each other. The viscosity of the solution must therefore rise, and this betrays itself by an increase in the time required for a certain volume of the colloid solution to flow through a standard capillary tube. Conversely, as the particles shrink the pure solvent is squeezed off, and so the viscosity must tend to fall back toward that of the pure solvent.

Wolfgang Pauli[6] has in this way studied blood serum from which the various admixed crystalloids have been removed by long dialysis against pure water. Such a solution is perfectly clear and stable. If its viscosity is measured it is found to be considerably higher than that of pure water owing to the colloid material in it. If a trace of acid is added the viscosity is enormously increased. But with progressive additions an upper limit is reached in the case of such acids as hydrochloric, hydrobromic, nitric or sulphuric, beyond which a further addition of acid does not further increase, but decreases viscosity. For the weaker organic acids, such as acetic, no such optimal point has

[1] Wolfgang Pauli: Pflüger's Arch., **67**, 219 (1897); ibid., **71**, 1 (1898); Hofmeister's Beit. z. chem. Physiologie, numerous papers in the years 1902 to 1908; Biochem. Zeitschr., **17**, 235 (1909); ibid., **18**, 340 (1909); ibid., **24**, 239 (1910). A general statement of his views is found in Kolloid-Zeitschr., **7**, 241 (1910).

[2] W. B. Hardy: Jour. Physiol., **24**, 288 (1899); ibid., **33**, 251 (1905); Proc. Royal Soc. London, Series B, **79**, 413 (1907); Zeitschr. f. physik. Chem., **33**, 385 (1900).

[3] P. von Schroeder: Zeitschr. f. physik. Chem., **45**, 75 (1903).

[4] Hans Handovsky: Fortschritte in der Kolloidchemie der Eiweisskörper, Dresden (1911), where references to his earlier papers will be found.

[5] K. Schorr: Cited by Pauli and Handovsky.

[6] Wolfgang Pauli: Naturwissensch. Rundschau, **21**, 3 (1906); Physical Chemistry in the Service of Medicine, 136, translated by M. H. Fischer, New York (1907). Pauli and H. Handovsky: Biochem. Zeitschr., **18**, 340 (1909).

yet been found. The addition of any salt to the acidified serum markedly reduces the viscosity. With the same salt the degree of reduction increases with the concentration of the salt. With a given concentration of any series of salts very different degrees of reduction in viscosity are obtained. Thus, when sodium salts are compared, the chlorid, nitrate and sulphocyanate are found to be less powerful than the acetate or sulphate, and in the order named. The addition of a non-electrolyte is conspicuously less effective in this regard. A practically identical series of findings has been established for the effects of alkali or of alkali plus various salts or non-electrolytes.

It is readily apparent that these statements are point for point analogous to those made previously regarding fibrin, gelatin and gluten, and hence justify the conclusion that *liquid (protein) colloids behave toward various external conditions in the same way as do the more solid ones.*

These changes in the swelling of fibrin, gelatin or gluten, or the viscosity changes of a liquid colloid, may opportunely be correlated here with changes in certain other properties. When acids, bases or salts are added to a protein colloid we observe variations not only in its swelling or viscosity, but in its precipitability or coagulability and in its optical behavior. What relation do these bear to each other? The fundamental change remains the same, namely, a change in the hydration capacity of the involved colloids. As already pointed out, whatever makes gelatin or fibrin swell increases viscosity, and *vice versa.* As the degree of hydration is increased, the intimacy of the colloid with its solvent is evidently increased, and so we should expect its stability to be increased. We are not surprised, therefore, to find that whatever increases hydration increases the stability of a colloid, while, conversely, whatever does the reverse favors instability, in other words, precipitation and coagulation. Thus, pure serum albumin is easily precipitated by heat or alcohol. When a little acid is added the hydration capacity of the colloid is increased and corresponding herewith, its precipitability through heat or alcohol is lost. But if yet more acid is added the hydration optimum is exceeded and now heat and alcohol regain their power of precipitating the protein. In a similar way the protein after being rendered non-precipitable through acid can again be precipitated by heat if a salt is added to the acid pro-

tein, for this again lowers the hydration capacity of the colloid.[1]

An analogous series of observations is available regarding changes in the optical behavior of protein colloids. We see from this that a series of reactions in certain protein colloids which at first seem to have nothing to do with each other are reducible in the end to a comparatively simple set of changes. And as we proceed we shall find that protoplasm, which is in essence but a colloid matrix of the type of fibrin, gelatin or blood serum, follows similarly simple laws. In the normal water content of a cell we shall see again a swollen colloid, and in œdema the same colloid swollen to a greater amount. Changes in the viscosity of the blood will come to mean changes in its degree of hydration, while corneal opacities in glaucoma and changes in the normal refraction and diffraction of the clear media will come to mean dehydration and precipitation of certain protein colloids present in the tissues of the eye.

7. On the Nature of the Increased and Decreased Hydration Capacity of the Proteins

While the theory of the increases and decreases in the water holding powers of the proteins is of no importance for the argument which follows, brief reference to its probable nature here[2] may serve to hold together in more easily grasped form the large number of isolated facts thus far detailed. Without referring to the theories advanced by other workers in this field (large portions of which are undoubtedly correct for certain aspects of the colloid chemistry of the proteins) our own opinion somewhat dogmatically framed may be thus expressed.

The pure proteins (as polymerized amino-acids) are the analogs

[1] The ordinary heat coagulation test for albumin in the urine makes use of these principles. The albumin is coagulated best when acid and salt are first added to the urine.

[2] For details and references to the literature see Martin H. Fischer, Marian O. Hooker, and George D. McLaughlin: Science, **48**, 143 (1918); ibid., **49**, 615 (1919): Chem. Engineer, **27**, 155, 184, 223, 253, 271 (1919); Jour. Lab. and Clin. Med., **5**, 207 (1920); ibid., **5**, 352 (1920); a running account is found in Martin H. Fischer: Soaps and Proteins, New York (1920), *in press*.

of the fatty acids. If we write the elementary constitution of a fatty acid as:

$$x-COOH$$

then that of an amino-(fatty) acid may be written:

$$\begin{array}{l} x-COOH \\ | \\ NH_2 \end{array}$$

the x standing for any nucleus we please. How now (remembering the fundamentals of the nature of the hydrophilic colloid state developed earlier[1]) do these act as solvents *for* water? Generally speaking, very poorly. The ordinary fatty acids (like oleic, lauric, palmitic, stearic) are generally said to take up no water at all (or, in our terminology, they do not "swell") and the same is largely true of the polymerized amino-acids which we call protein. Casein, for example, sinks as a non-sticky, white powder to the bottom of a vessel of water; fibrin and gelatin do absorb some water as evidenced in the experiments described above.

As soon, however, as an alkali is added to a fatty acid, soap is formed which, as a new compound, is also a better solvent for the water. Were we ignorant of the chemical union that had taken place we would say that "the hydration capacity of the fatty acid had been increased" through the addition of the alkali. Actually the fatty acid has been replaced by soap and the "increased swelling" is due to the better solvent properties of the latter *for* water. Things are identical if protein replaces the pure fatty acid. A "soap" is again formed and hence the greater swelling of casein, fibrin, gelatin, gluten or aleuronat when an alkali is added to them.

The power for thus taking up water varies, however, with the type of base introduced into a given fatty acid (in other words with the kind of soap formed), and in about the following order when the base yielding the highest hydration capacity is given first:

NH_4, K, Na, Li, Mg, Ca, Ba (?), Pb, Fe, Hg.

It will be remembered that this is also the order in which different hydroxids (irrespective of their dissociation values and hydroxyl ion concentrations) affect the swelling of various proteins.

[1] See page 50.

There exists, however, an interesting chemical difference between the fatty acids and the amino-(fatty) acids which we call proteins. This is expressed in the possession by the latter of the NH_2 group. While the former are purely " acid " in character, the latter are not only acid but alkaline as well, or, as commonly expressed, *amphoteric*. While the fatty acids can be treated only with an alkali to yield new compounds, the amino-(fatty) acids can be treated not only with this but with an acid as well. Against the one series of compounds yielded by the fatty acids we can produce at least two in the case of the amino-acids. Depending upon the acid used we can make the chlorids, bromids, iodids, sulphates, tartrates and citrates out of " neutral " casein, fibrin, gelatin, gluten or aleuronat. These substances (salts) again have a higher hydration capacity than the pure proteins, and hence the reason why all acids added to any pure protein increase its hydration capacity. But these hydration capacities again differ with the different acid radicals, and hence the statement that hydrochloric acid is a more powerful swelling agent than acetic, this than sulphuric, etc.

How now may we understand the hydrating effects of neutral compounds, like sodium chlorid, upon substances like gelatin or fibrin and the lack of such effects when magnesium chlorid or sulphate is used? Compounds are again formed (after the hydrolysis of the salts in the water) yielding in the first instance sodium-protein-chlorid, in the second magnesium-protein-chlorid or magnesium-protein-sulphate. The first is a better solvent for water than the pure protein; the second an even worse one.

The action of substances like urea, pyridin and the amins is somewhat more complicated but the formation of new compounds with different solvent capacities *for* water is again a fundamental factor. These compounds are not, however, of the simple type resulting when (acids or) alkalies are used, as already apparent from the fact that the addition of acid or neutral salt does not reduce their swelling as anticipated, while sugars do this in a degree unexpected in simple (acid or) alkali proteinates.

How now may be understood the effects of the addition of any neutral salt to an acid or alkali proteinate? First to be considered is the chemical possibility of replacing the acid or base of the proteinate by one of the radicals of the added salt. To replace a sodium radical by potassium or an acetate radical by a chlorid is

to increase the swelling capacity; to replace them by magnesium or a sulphate radical is to decrease the swelling capacity. But where such chemical interchange is out of the question, as when sodium chlorid is seen to reduce the swelling of an alkalinized protein (sodium proteinate) what is it that happens then? *The salt affects the solvent, namely, water.* The neutral salt combines with water, as first insisted upon by Franz Hofmeister, and the protein mass is deprived of its "solvent" by this amount. Or, put in another way, the protein compound is a poorer solvent for salt-water than for pure water.

It must be remembered, finally, that these remarks cover only *one aspect* of the colloid behavior of systems in which protein appears, albeit the most important one for the *normal* physiology of protoplasm. This, as we shall see, is essentially nothing but a solution of water *in* protoplasmic material. Another aspect of the whole problem, namely, that of the solubility of protein *in* water, is returned to later.[1]

III

THE ANALOGY BETWEEN THE SWELLING OF CERTAIN PROTEIN COLLOIDS AND THE SWELLING OF PROTOPLASM

Having become familiar with the effect of various external conditions on the swelling of several simple so-called hydrophilic colloids (fibrin, gelatin, gluten, aleuronat, blood serum), we have at our disposal some facts which we may utilize in an attempt to analyze the ways and means by which tissues hold their normal amount of water, and to discover how under altered external conditions they may come to hold more or less than is considered normal. It is evident that could we show that the same conditions which make fibrin, gelatin or gluten take up and give off water, affect protoplasm similarly, a real step forward in the solution of this problem of the absorption and secretion of water by the tissues would be made. This can be done and with great simplicity. As the following paragraphs show, *the absorption of water by various tissues is entirely analogous to the absorption of water by fibrin, gelatin, gluten or aleuronat.*

[1] See page 509.

1. The Analogy between the Absorption of Water by Certain Protein Colloids and by Muscle

Simple facts regarding the absorption of water by various cells and tissues are very numerous and date back to the earliest periods of modern physiology. We shall have occasion to review them later. So far as water absorption by *muscle* is concerned, O. Nasse[1] studied this question from an osmotic standpoint as far back as 1869, and E. Brücke[2] touched some aspects of the problem even earlier. Most of the investigations of this particular type of tissue made since then are useless for our purposes because they antedate the years in which adequate use of the principles of physical chemistry first began to be made in biological studies. The period of interest to us begins with 1898, when Jacques Loeb[3] published the results of some experiments on the influence of acids, alkalies and various salts on the absorption of water by the gastrocnemius muscle of the frog. He found that muscle absorbs much water if placed in distilled water or in solutions of various acids or alkalies. From his earlier experiments he concluded that a muscle does not change in weight if kept in a solution having an osmotic pressure equal to that of the blood, but that it gains or loses weight if placed in solutions having respectively a lower or a higher osmotic pressure. About the same conclusion had been previously reached by Nasse. But Nasse noted that certain salts, notably the sulphates, bromids and iodids, exhibited a greater than calculated "osmotic" effect. Loeb made a similar observation when he discovered that in spite of isosmoticity a frog's muscle will absorb more water from a potassium chlorid solution than from one of sodium chlorid, and more from this than from one of calcium chlorid. The analogy between the latter fact and the absorption of water by potassium, sodium and calcium soaps was pointed out, but our conceptions of the colloids had not at that time advanced to the point of recognizing in the soaps examples of this class of bodies. As much controversy has hedged about the question of the historical

[1] O. Nasse: Pflüger's Arch., **2**, 97 (1869).

[2] E. Brücke: Sitzungsber. d. math. Naturw. Cl. d. kais. Akad. d. Wissensch., **55**, 622 (1867).

[3] Jacques Loeb: Pflüger's Arch., **69**, 1 (1898); ibid., **71**, 457 (1899); bid., **75**, 303 (1899).

development of the colloid chemical theory of water absorption by protoplasm it is well to emphasize that LOEB not only never contributed anything to its establishment, but actually thrust such aside.[1] The action of acids and alkalies on muscle LOEB brought into harmony with the then current osmotic conceptions of absorption by assuming that they induced changes within the muscle tissues whereby the osmotic pressure of the cell contents was raised, as previously emphasized for a series of other animal tissues by H. J. HAMBURGER,[2] C. VON LIMBECK,[3] GÜRBER[4] and C. EIJKMAN.[5]

The experiments of RALPH W. WEBSTER[6] and E. OVERTON[7] followed those of LOEB. WEBSTER concluded that osmotic effects could only explain the absorption from water and solutions of cane sugar. His careful study of the effects of electrolytes showed unequivocally that simple osmotic effects are out of the question here. OVERTON came to essentially the same conclusion and attempted to help out the problem by his conception of lipoid membranes about living cells and their entire impermeability to salts. He showed conclusively that LOEB's explanation of the action of acids and alkalies cannot be correct, for were

[1] LOEB: Pflüger's Arch., **77**, 305 (1899) says: "The analogy between the absorption of water by soaps and by muscle is of importance in explaining the mechanism of water-absorption. The majority of authors, for example, HOFMEISTER, assume that in the absorption of fluids by tissues we deal with imbibition; that is to say, with capillary phenomena. But in the absorption of fluid by soaps we deal with solution phenomena. The forces active here are osmotic and not the surface tension forces active in capillary phenomena." (In Bezug auf die Mechanik der Flüssigkeitsresorption ist die Analogie zwischen dem Verhalten von Seifen und dem Muckel von Bedeutung. Die Mehrzahl der Autoren, z. B. HOFMEISTER, nehmen an dass es sich bei der Resorption von Flüssigkeiten in Geweben um Imbibition handle, d. h. um Capillaritätserscheinungen. Bei der Flüssigkeitsaufnahme in Seifen handelt es sich aber un Lösungsvorgänge. Die dabei maasgebenden Kräfte sind osmotische Drucke und nicht die bei capillaren Vorgängen maasgebenden Oberflächenspannungen.)

[2] H. J. HAMBURGER: Arch. f. (Anat. u.) Physiol., 513 (1892); ibid., 153 (1893); Zeitschr. f. Biol., **35**, 252 and 280 (1897), where references to his earlier papers are found. See also Arch. f. (Anat. u.) Physiol., 31 (1898).

[3] C. VON LIMBECK: Arch f. exp. Path. u. Pharm., **35**, 309 (1894).

[4] GÜRBER: Sitzberich. d. med. phys. Gesellsch., Würzburg, Feb. 25 (1895).

[5] C. EIJKMAN: Virchow's Arch. f. path. Anat., **143**, 448 (1896), where references to his earlier papers will be found.

[6] RALPH W. WEBSTER: University of Chicago Decennial Publications, **10** (1900); cited from a reprint.

[7] E. OVERTON: Pflüger's Arch., **92**, 115 (1902).

all the proteins, carbohydrates and fats contained in muscle, split into their simplest digestion products they would still not yield a sufficient number of molecules to account, through conceptions of osmotic pressure, for the amount of water absorbed by muscle in the solution of an acid or an alkali. To certain other of OVERTON's ideas we shall have occasion to return later.

Both in individual experimental results and in the conclusions drawn from them there exist many contradictions between the findings of these various authors. It is needless to touch upon them in detail. For a majority of these differences an explanation can readily be found. None of the authors mentioned ever studied the *curves* of absorption of water by muscle under various conditions. They weighed their muscles at arbitrary intervals of time, and drew their conclusions from these weighings—at times only one weighing. A moment's study of a few of the curves which accompany these paragraphs will show how wrong this is. (See Figs. 61 to 63.) To cite but one example, a muscle kept in any salt solution need not, and, in fact, usually does not, show a progressive increase or decrease in weight. It may at first show a very decided decrease and later an equally decided increase; or the reverse may be the case. If this fact is borne in mind, many of the statements made by these authors and not in harmony with each other or with my own experimental results will find a ready explanation.

We shall turn now to the conclusions to which I have been led from my own experiments, and see if in them we may not find an acceptable explanation of the apparently unattached and not easily accounted for facts observed by the previous workers in this field. My experiments were made with the hind legs of tree toads (Hyla) from which the skin had been removed, and with the gastrocnemius muscles of the frog (Rana). The muscle preparations were carefully dried, weighed and placed in various solutions contained in lightly covered finger bowls. At various intervals they were removed from the solutions, carefully dried with filter paper, and weighed, and the amount of water they had lost or gained was calculated in per cent of the original weight of the muscle. From many such experiments the following conclusions of importance to the subject in hand were drawn. The conclusions are again lettered so as to permit ready comparison with similarly lettered and corresponding conclusions

reached in the study of the absorption of water by fibrin, gelatin, gluten and aleuronat.

(*a*) A muscle swells more in the solution of any acid than it does in pure water, but the amount of this swelling is greater in some acids than in others. Muscle swells most in a hydrochloric acid solution, almost as much in a nitric acid solution of the same concentration, and less in acetic and sulphuric acids in the order named. Fig. 57 may serve as an illustration of this

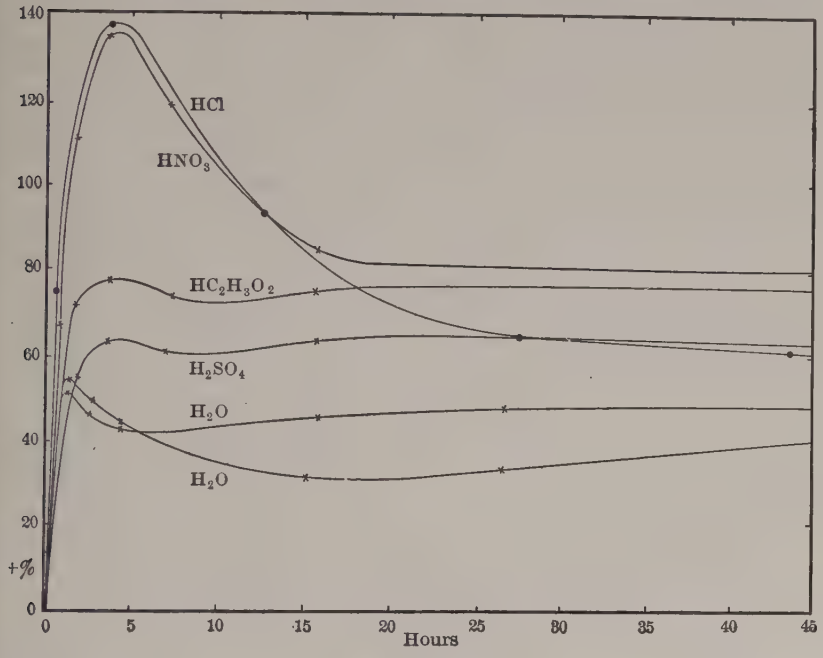


FIGURE 57.

fact. The experiments upon which these curves are based were made with the hind legs of tree toads (Hyla) from which the skin had been removed.[1]

An important relationship exists between the concentration of the acid employed and the amount that the muscle swells. This is readily apparent in Fig. 58 and Table LXIV, which contains the experimental findings from which the curves were constructed. In this series of experiments the gastrocnemius muscles of frogs (Rana) were used. There is first to be noted

[1] MARTIN H. FISCHER: Pflüger's Arch., **124**, 69 (1908).

an increase in the swelling with every increase in the concentration of the acid. But after a time a point is reached beyond

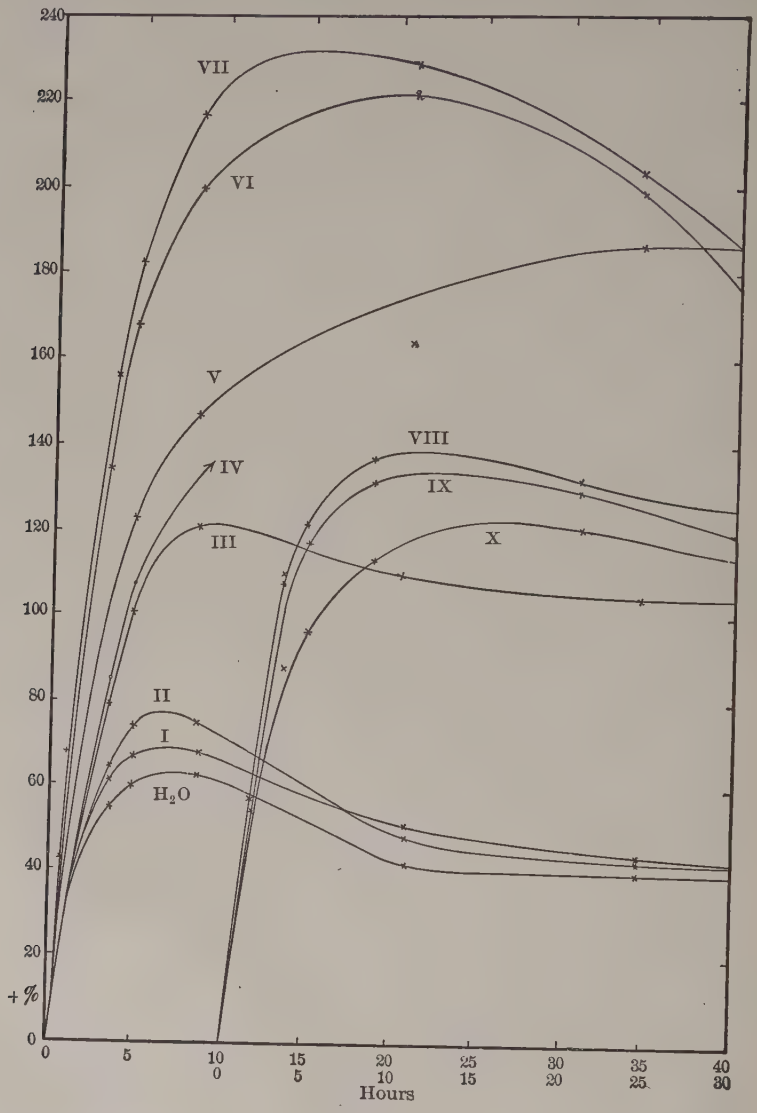


FIGURE 58.

which a further increase in concentration is followed by a diminished absorption of water. This fact has its analog in the

TABLE LXIV

Gastrocnemius Muscles of the Frog

Hours in the solution.	110 cc. H_2O.	1/4 cc. n/10 HCl + 109¾ cc. H_2O.	1/2 cc. n/10 HCl + 109½ cc. H_2O.	1 cc. n/10 HCl + 109 cc. H_2O.	2 cc. n/10 HCl + 108 cc. H_2O.	3 cc. n/10 HCl + 107 cc. H_2O.
	%	%	%	%	%	%
0	0.582 (0)	0.599 (0)	0.596 (0)	0.568 (0)	0.430 (0)	0.448 (0)
1.05	0.790 (+35.7)	0.829 (+38.4)	0.815 (+35.1)	0.781 (+ 34.0)	0.650 (+ 27.8)	0.699 (+ 56.0)
3.25	0.905 (+55.5)	0.965 (+61.1)	0.967 (+62.2)	1.015 (+ 78.6)	0.793 (+ 84.4)	0.915 (+104.2)
4.45	0.930 (+59.8)	0.990 (+65.2)	1.035 (+73.0)	1.137 (+100.1)	0.889 (+106.7)	0.999 (+123.1)
8.45	0.940 (+61.5)	0.998 (+66.6)	1.031 (+72.9)	1.259 (+121.6)	0.961 (+123.4)	1.102 (+146.0)
20.50	0.854 (+41.6)	0.908 (+51.6)	0.889 (+49.1)	1.200 (+111.2)	1.110 (+158.1)	1.178 (+162.9)
34.10	0.820 (+40.9)	0.860 (+43.5)	0.850 (+42.6)	1.165 (+105.1)	1.345 (+212.7)	1.280 (+185.6)
45.50	0.810 (+39.2)	0.850 (+41.9)	0.845 (+41.7)	1.155 (+103.3)	1.410 (+227.9)	1.260 (+181.2)
70.20	0.818 (+40.0)	0.835 (+39.4)	0.830 (+39.2)	1.170 (+106.0)	1.425 (+231.4)	1.075 (+139.9)
	(a)	(b)	(c)	(c)	(d)	(d)
		I	II	III	IV	V

Hours in the solution.	4 cc. n/10 HCl + 106 cc. H_2O.	5 cc. n/10 HCl + 105 cc. H_2O.	8 cc. n/10 HCl + 102 cc. H_2O.	9 cc. n/10 HCl + 101 cc. H_2O.	10 cc. n/10 HCl + 100 cc. H_2O.
	%	%	%	%	%
0	0.491 (0)	0.541 (0)	0.723 (0)	0.686 (0)	1.021 (0)
1.05	0.815 (+ 65.9)	0.960 (+ 43.6)	1.138 (+ 57.4)	1.072 (+ 56.2)	1.520 (+ 48.8)
3.25	1.150 (+134.2)	1.387 (+156.3)	1.500 (+107.4)	1.435 (+109.1)	1.915 (+ 87.5)
4.45	1.313 (+167.4)	1.532 (+183.1)	1.595 (+120.6)	1.505 (+119.4)	2.008 (+ 96.6)
8.45	1.473 (+200.0)	1.720 (+217.9)	1.710 (+136.5)	1.586 (+131.1)	2.172 (+112.7)
20.50	1.578 (+221.3)	1.780 (+229.0)	1.675 (+131.6)	1.582 (+129.9)	2.248 (+120.1)
34.10	1.420 (+189.6)	1.650 (+204.9)	1.632 (+125.7)	1.458 (+112.5)	2.160 (+111.8)
45.50	1.220 (+148.4)	1.480 (+173.8)	1.585 (+119.2)	1.455 (+112.1)	2.130 (+109.5)
70.20	1.095 (+123.0)	1.285 (+137.5)	1.540 (+113.0)	1.370 (+ 99.7)	2.070 (+102.6)
	(e)	(e)	(f)	(f)	(g)
	VI	VII	VIII	IX	X

c, c, d, d, etc., indicate opposite muscles of same frog.

absorption of water by fibrin or gelatin in acid solutions of various concentrations.

Table LXIV is given in detail to show by what means were obtained all the data upon which conclusions in this section are based. The first figure in each of the columns indicates the original weight of the muscle. After each of the weighings there is given, in parentheses, the gain in weight, expressed in per cent of the original weight of the muscle.

(*b*) It is somewhat difficult to say what is the effect of alkalies on the absorption of water by muscle. The statement is unquestionably true that muscle swells more in the solution of any alkali than in water. There seems to be a great difference, however, both in the swelling of tree toad legs from which the skin has been removed and of the gastrocnemius muscles of frog with the season. In my original experiments with tree toads I got a decidedly greater swelling in dilute alkaline solutions than in water. In later experiments (December 11, 1908) with the gastrocnemius muscles of winter frogs (Rana) this difference was not so marked. I append Tables LXV and LXVI to illustrate this point. In explanation of these results it should be noted that the amount of swelling in pure water runs unusually high. As, to my mind, this is brought about chiefly through the production of acid within the muscles, the high water absorption values indicate an unusually large production of acid (starvation acidosis in winter frogs?). When such muscles are placed in alkaline solutions, the alkali combines with the acid, and the salt

TABLE LXV

GASTROCNEMIUS MUSCLES OF THE FROG

Hours in the solution.	110 cc. H_2O.	5 cc. n/10 NaOH + 105 cc. H_2O.	10 cc. n/10 NaOH + 100 cc. H_2O.
	%	%	%
0	0.984 (0)	0.571 (0)	0.571 (0)
1.05	1.397 (+41.9)	0.858 (+50.2)	0.920 (+ 61.1)
3.25	1.610 (+63.6)	0.995 (+56.7)	1.104 (+ 93.3)
4.45	1.659 (+68.5)	0.881 (+54.3)	1.144 (+100.3)
8.45	1.680 (+70.7)	0.854 (+49.5)	1.141 (+ 99.8)
20.50	1.626 (+65.2)	0.842 (+47.4)	1.108 (+ 94.0)
34.10	1.540 (+56.5)	0.838 (+45.9)	1.125 (+ 97.0)
45.50	1.530 (+55.4)	0.850 (+48.1)	1.142 (+100.0)
70.20	1.510 (+53.4)	0.885 (+54.9)	1.135 (+ 98.7)

TABLE LXVI

Gastrocnemius Muscles of the Frog

Hours in the solution.	110 cc. H_2O.	1/4 cc. n/10 NaOH+109-3/4 cc. H_2O.	1/2 cc. n/10 NaOH +109-1/2 cc. H_2O.	1 cc. n/10 NaOH +109 cc. H_2O.	2 cc. n/10 NaOH +108 cc. H_2O.	3 cc. n/10 NaOH +107 cc. H_2O.	4 cc. n/10 NaOH +106 cc. H_2O.
	%	%	%	%	%	%	%
0	0.808 (0)	0.732 (0)	0.706 (0)	0.704 (0)	0.609 (0)	0.608 (0)	0.595 (0)
1.00	1.104 (+36.6)	1.022 (+39.6)	0.970 (+37.4)	0.972 (+38.0)	0.882 (+44.8)	0.905 (+48.8)	0.852 (+43.2)
3.50	1.265 (+56.5)	1.150 (+57.1)	1.090 (+54.4)	1.106 (+57.1)	0.900 (+47.8)	0.893 (+46.87)	0.875 (+48.7)
6.35	1.300 (+73.2)	1.170 (+59.8)	1.100 (+55.8)	1.120 (+59.1)	0.860 (+41.2)	0.870 (+43.1)	0.840 (+48.7)
8.50	1.290 (+59.6)	1.155 (+57.8)	1.072 (+51.8)	1.102 (+56.5)	0.849 (+38.0)	0.855 (+40.6)	0.818 (+37.5)
11.30	1.260 (+55.9)	1.130 (+54.3)	1.048 (+48.4)	1.070 (+51.9)	0.858 (+40.8)	0.865 (+42.1)	0.820 (+37.8)
24.30	1.135 (+40.4)	1.030 (+40.7)	0.950 (+34.5)	0.975 (+38.5)	0.884 (+45.1)	0.908 (+49.3)	? ?
34.50	1.140 (+41.0)	1.032 (+40.9)	0.970 (+37.4)	0.995 (+41.2)	0.920 (+51.0)	0.935 (+53.78)	0.872 (+46.5)
58.45	1.130 (+39.8)	1.028 (+40.4)	0.965 (+36.7)	1.000 (+42.0)	0.920 (+51.0)	0.935 (+53.78)	0.875 (+47.0)
82.40	1.130 (+39.8)	1.015 (+38.6)	0.965 (+36.7)	1.040 (+47.7)	0.925 (+52.0)	0.940 (+54.6)	0.885 (+48.7)

Hours in the solution.	5 cc. n/10 NaOH +105 cc. H_2O.	6 cc. n/10 NaOH +104 cc. H_2O.	7 cc. n/10 NaOH +103 cc. H_2O.	8 cc. n/10 NaOH +102 cc. H_2O.	9 cc. n/10 NaOH +101 cc. H_2O.	10 cc. n/10 NaOH +100 cc. H_2O.	110 cc. H_2O.
	%	%	%	%	%	%	%
0	0.580(0)	0.558 (0)	0.547 (0)	0.545 (0)	0.537 (0)	0.461 (0)	0.447 (0)
1.00	0.885 (+52.6)	0.818 (+46.5)	0.795 (+45.3)	0.890 (+63.3)	0.778 (+44.8)	0.675 (+46.4)	0.655 (+46.5)
3.50	0.918 (+58.3)	0.822 (+47.3)	0.835 (+52.6)	0.935 (+71.5)	0.813 (+51.4)	0.710 (+52.0)	0.715 (+59.9)
6.35	0.900 (+55.2)	0.795 (+42.5)	0.820 (+49.9)	0.910 (+66.9)	0.795 (+48.0)	0.680 (+47.5)	0.705 (+57.7)
8.50	0.880 (+51.7)	0.789 (+41.0)	0.802 (+46.6)	0.912 (+67.3)	0.796 (+48.2)	0.670 (+45.3)	0.680 (+52.1)
11.30	0.855 (+47.4)	0.770 (+37.8)	0.800 (+46.2)	0.900 (+65.1)	0.778 (+44.9)	0.660 (+43.1)	0.642 (+43.6)
24.30	0.825 (+42.2)	0.845 (+51.4)	0.790 (+44.4)	0.920 (+68.8)	0.825 (+53.6)	0.670 (+45.3)	0.605 (+35.3)
34.50	0.880 (+51.7)	0.825 (+47.8)	0.840 (+53.5)	0.990 (+81.6)	0.870 (+58.0)	0.725 (+57.2)	0.620 (+38.7)
58.45	0.900 (+55.2)	0.830 (+48.7)	0.860 (+57.2)	1.020 (+87.1)	0.910 (+69.5)	0.755 (+63.7)	0.610 (+36.4)
82.40	0.900 (+55.2)	0.845 (+51.4)	0.863 (+57.5)	1.030 (+88.9)	0.925 (+72.2)	0.772 (+67.4)	0.605 (+35.3)

formed by the union inhibits the swelling. (See paragraph *c*, below.)

Loeb states that the gastrocnemius muscles of frogs swell more in the solution of an alkali than in acid solutions of the same normality. The few weighings that he gives are not sufficient to prove this, for only serial weighings can tell us whether the maximal swelling in a muscle has been attained, is being approximated, or

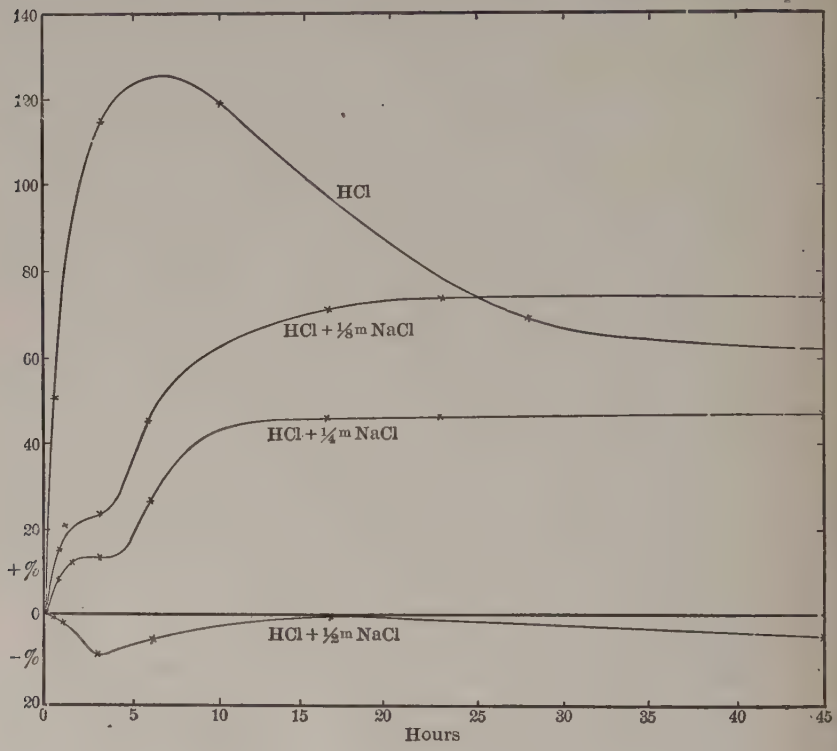


Figure 59.

has been passed. The experiments just outlined indicate that, if the opposite is not true, the question is at least still an open one.

(*c*) The addition of any salt to the solution of an acid decreases the amount that a muscle will swell in that solution, and the higher the concentration of the salt the greater is the amount of this inhibition. Fig. 59 illustrates this fact. The curve marked HCl was obtained by immersing a gastrocnemius muscle in a solution of hydrochloric acid, made by adding 10 cc. n/10 hydro-

chloric acid to 100 cc. of water. The three remaining curves show the changes in weight suffered by muscles immersed in solutions made by adding the same amount of acid to 100 cc., respectively, of m/8, m/4 or m/2 solutions of sodium chlorid. As plainly evident, the action of the hydrochloric acid is entirely inhibited,

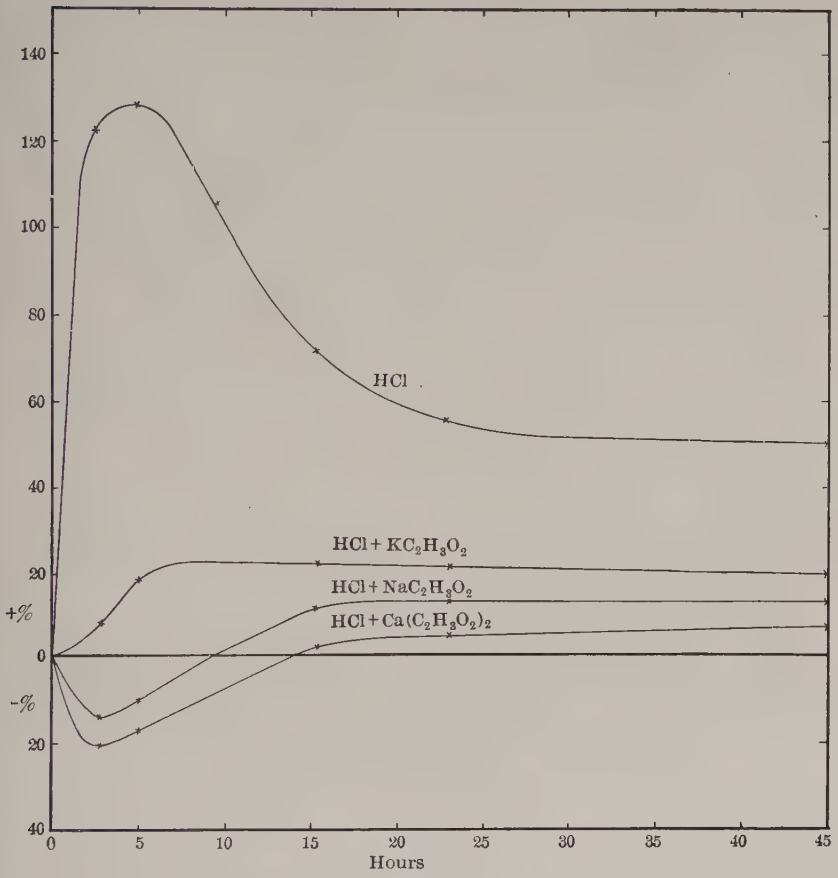


FIGURE 60.

so far as the absorption of water is concerned when the last-named concentration of sodium chlorid is employed.

(*d*) While all salts diminish the amount of water absorbed by muscle in an acid solution, the different salts are very unequally effective in this regard, when equimolar solutions are compared. The effect of three acetates on the swelling of tree-toad muscu-

lature is compared in Fig. 60. The upper curve represents the action of a pure n/110 hydrochloric acid solution, made by adding 10 cc. n 10 hydrochloric acid to 100 cc. water; the remaining curves, the effect when the same amount of acid is added, respectively, to 100 cc. m/4 solutions of potassium, sodium and calcium

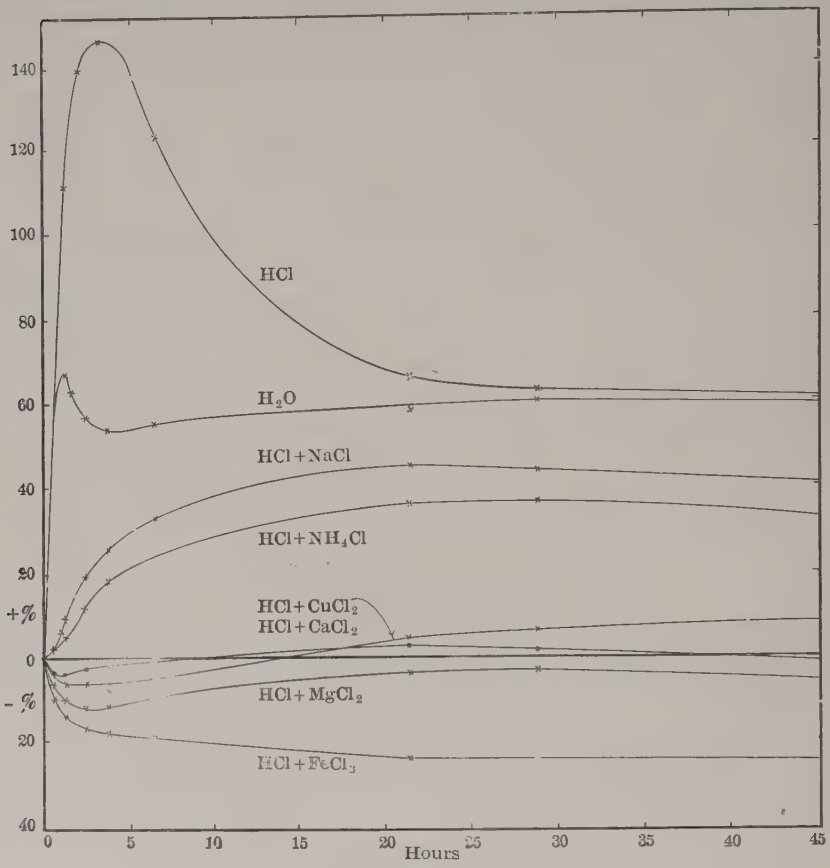


FIGURE 61.

acetate. These salts are effective in reducing the amount of swelling in the order named, potassium being less powerful than sodium, and this than calcium. It will be remembered that we found the same arrangement when the action of different salts with a common acid radical on the swelling of fibrin in acid solutions was compared.

In Fig. 61 are compared the effects of a series of chlorids on

the swelling of muscle in acid solutions. The hydrochloric acid curve stands prominently above that for pure water. All the salts bring about a diminution in the amount of swelling, but while present in the same molar concentration they are very differently effective in this regard. The solutions were all prepared by adding 10 cc. n/10 hydrochloric acid to 100 cc. m/4 solutions of the various salts. We have no difficulty in recognizing the following order in which the diffe en' basic radicals are effective, that producing the least inhibition being given first:

Sodium, Ammonium, Calcium, Copper (ic), Magnesium, Iron (ic).

With the exception of the copper salt the general grouping is again similar to that found in studying the effects of different salts on the swelling of fibrin and gelatin. That the arrangement of the individual radicals is not identical in the two series is not surprising, for muscle represents not only a mixture of several colloids, but contains several salts. It is, therefore, from both a physical and a chemical standpoint a substance not nearly so well defined as washed fibrin or gelatin.

Fig. 62 permits the comparison of a few acid radicals. The curves for hydrochloric acid and for water need no special comment. The solutions containing salts were again prepared by adding 10 cc. n/10 hydrochloric acid to 100 cc. of the m/4 solutions of the required ammonium salts. The order,

Acetate, Chlorid, Nitrate, Sulphate,

in which the radical least effective in reducing the swelling in an acid solution is named first, is readily recognized. The general grouping is here again the same as in the case of fibrin.

The relations in muscle are not, however, all as simple as might at first appear from this analogy between the swelling of fibrin and the swelling of muscle. Fig. 63 has been introduced in illustration of this fact. A number of acid radicals may here be compared, but as apparent, the order in which this series of sodium salts is effective is not an easy one to describe. We recognize in the first few hours of the experiment the order familiar to us from our study of fibrin,

Chlorid, Sulphate, Phosphate, Tartrate,

but in the later hours this is changed to

Tartrate, Phosphate, Chlorid, Sulphate.

The causes for this change are not as yet clear. They are undoubtedly several in number, dependent in part on differences in the rate of diffusion of acids, salts, etc., into and out of the muscles; in part, on the fact that muscle after removal from the body undergoes spontaneously a series of chemical changes through which its physical state is progressively altered. This series of curves shows well the dangers inherent in conclusions based upon single or too few weighings of muscle at arbitrarily chosen intervals.

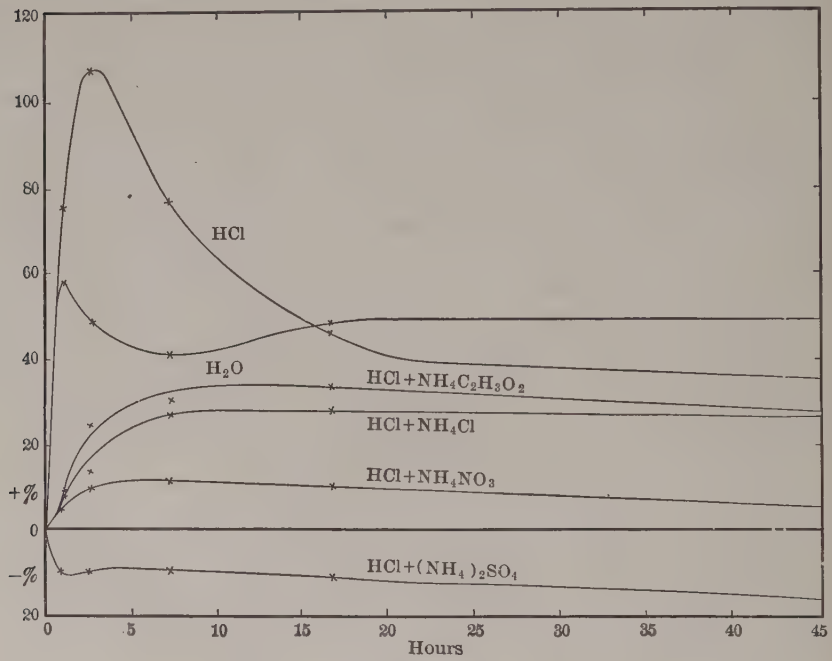


FIGURE 62.

(*e* and *f*) The marked effect of all electrolytes in reducing the swelling of a muscle in an acid solution is not shared by non-electrolytes. Fig. 64 shows this better than many words. None of the curves shows any characteristic change in shape from the pure hydrochloric acid curve in spite of the fact that the various non-electrolytes are present in amounts *osmotically* more than equal to those of the electrolytes used in the already described experiments. In each case 10 cc. n/10 hydrochloric acid were

added to 100 cc. m/2 cane sugar, ethyl or methyl alcohol, urea or glycerin. The two monatomic alcohols seem to be entirely without effect in the concentrations employed. Glycerin produces some inhibition of swelling. The urea curve lies well above that for glycerin. The general order in which these non-electrolytes affect swelling is therefore again similar to that observed in studying the swelling of fibrin or gelatin.

(*g*) The taking up and giving off of water by muscle represents in large part a reversible process. This process, however, is not completely reversible (within the time limits of these experi-

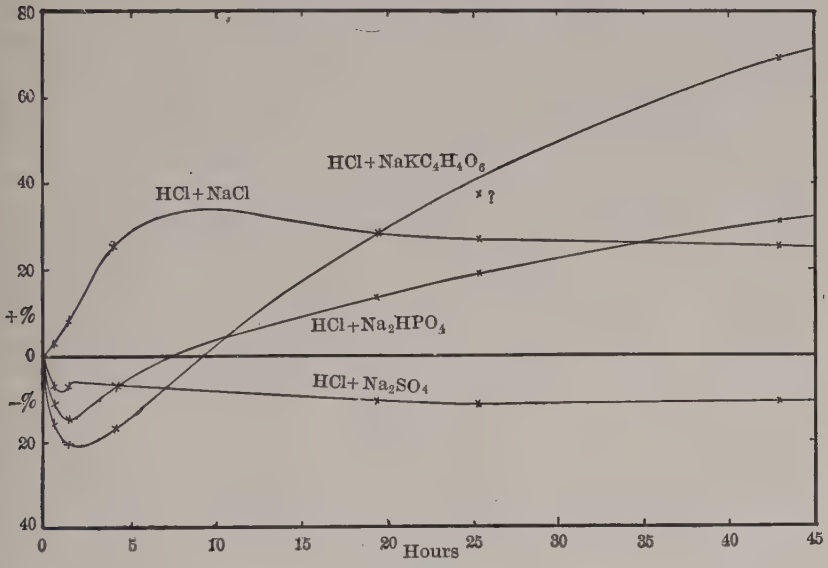


FIGURE 63.

ments) in that a muscle seems to suffer somewhat permanently from every condition through which it is required to pass. This statement, which is analogous to that made regarding fibrin, is illustrated in Fig. 65. The first part of the curve *a*, *a*, *a*, represents the stage of progressive loss of water by a gastrocnemius muscle which has passed the point of maximal swelling in a solution of n/110 hydrochloric acid. At the place indicated by the arrow it is transferred to pure water, in which the muscle is observed to gain promptly in weight and so to continue for some hours. An explanation of this fact is found when we look at Fig. 58 and Table LXIV. A n/110 hydrochloric acid does

not represent the optimal concentration for the swelling of a frog's muscle. To transfer it from such to pure water is to place it, at least for a time, under conditions which approximate the optimal more nearly (an acid solution below the concentration of n/110).

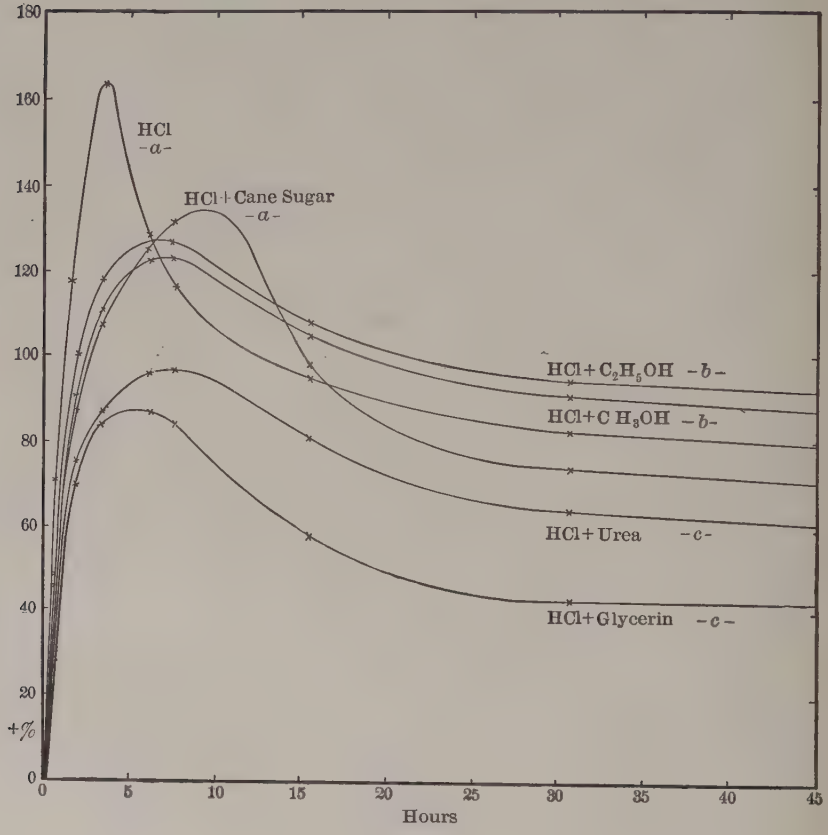


FIGURE 64.

Curve *b*, *b*, *b*, *b*, represents the effect of transference from a mixture of acid and potassium chlorid to one of acid and calcium chlorid, and finally into a pure hydrochloric acid solution. While the muscle was steadily increasing in weight in the HCl-KCl mixture, it began to lose immediately after transfer to the HCl-$CaCl_2$ mixture. When taken out of this and placed in pure

HCl, a gain is noted, but this is not sufficient to make the muscle even approximate in weight that originally attained in the HCl-KCl mixture—the muscle recovers only partially from the effect of its residence in the hydrochloric acid solution containing calcium chlorid.

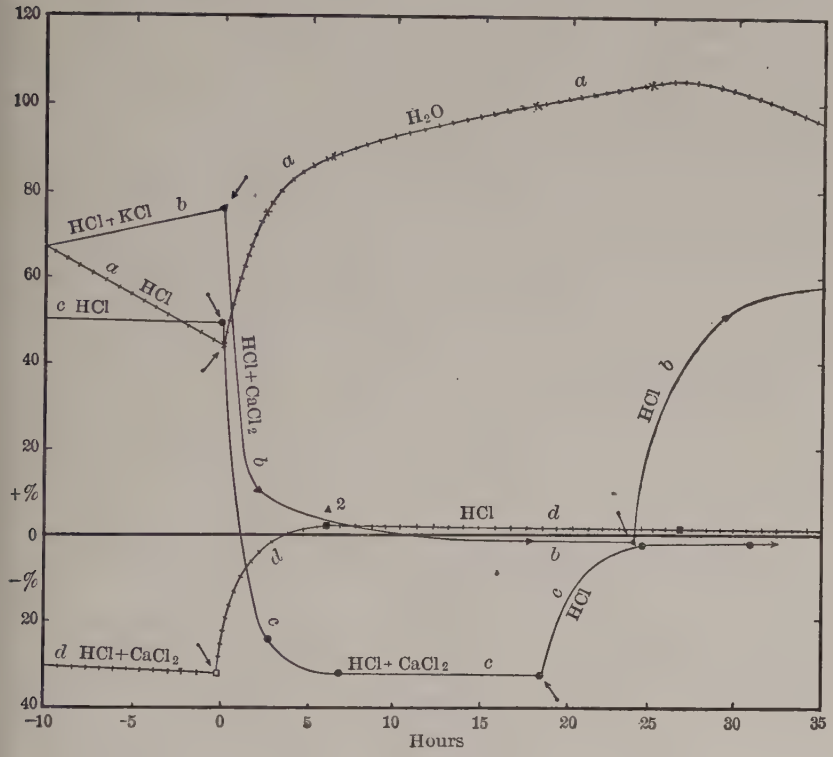


FIGURE 65.

Curve *c, c, c, c,* indicates also the somewhat lasting effect upon the muscle of every condition through which it passes. The sharp fall in weight upon transference from the pure n/110 hydrochloric acid to the equally concentrated one containing calcium chlorid (10 cc. n/10 HCl+100 cc. m/2 $CaCl_2$) and the only incomplete restitution when returned to the pure acid solution is clearly evident in the drawing.

In curve *d, d, d,* is found additional evidence for the incomplete reversibility of the absorption and secretion of water by muscle.

The muscle had steadily lost in weight since being placed in a mixture of 10 cc. n/10 HCl+100 cc. m/2 $CaCl_2$ when at the point indicated by the arrow it was transferred to pure n/110 hydrochloric acid. The muscle began to gain immediately, but owing to previous residence in the solution containing calcium chlorid this gain amounted to little more than a restoration of its original weight.

These paragraphs suffice to prove that the absorption and secretion of water by such a tissue as muscle is identical with the absorption of water by various protein colloids from a *qualitative* point of view. We must now consider the *quantitative* aspects of the problem; in other words, prove that the absorption of water by such a colloid as fibrin or gelatin is of sufficient magnitude to account, without strain, for the maximal amounts ever absorbed by muscle. The largest amount of water that I ever found muscle to take up was less than two and one-half times its original weight (246.6 per cent). As fresh muscle contains about 75 per cent water and about 1 per cent ash, we may say, roughly, that one-fourth consists of various organic substances. These belong, nearly all of them, to the colloids, and to that special half of them known as lyophilic (hydrophilic) or emulsion colloids. On the basis of these figures one gram of *dried* muscle substance is equivalent to four grams of moist (normal) muscle, which has the power of absorbing enough water (250 per cent) to weigh fourteen grams. One part of *dry* muscle substance may therefore absorb thirteen times its weight of water. How easily this, which represents the extreme of water absorption in muscle, may be accounted for through the power of simple colloids to absorb water, is apparent when it is remembered that fibrin readily absorbs fifteen to twenty times its weight of water in dilute acids and as much as thirty (under the best circumstances almost forty) times its weight in dilute alkalies. The maximal values obtained with gelatin run even higher. It absorbs without difficulty even sixty-five times its weight of water.

This extensive analogy between the absorption of water by fibrin or gelatin and the absorption of water by muscle, both from a quantitative and a qualitative standpoint, seems to me to justify the conclusion that *the absorption of water by muscle is determined in the main by the state of the colloids contained in it.*

But since muscle is only a tissue chosen at random for study, the question arises whether the absorption of water by *all* tissues is simply a function of the colloids they contain. We shall next attempt to answer this larger question.

2. The Analogy between the Absorption of Water by Certain Protein Colloids and by the Eye

The eye consists, as is well known, of a series of different tissues each characterized by distinctive physical characteristics. There is no difficulty in distinguishing between the opaque sclera, the clear and transparent cornea, the well-named "glass-like" vitreous and the lens. The eye, in consequence, represents a collection of tissues which may be utilized as experimental material in our attempt to see if the analogy between the absorption of water by certain colloids and the absorption of water by muscle, cannot be broadened to embrace an analogy between the absorption of water by these colloids and the absorption of water by protoplasm in general.

The following experiments show that *the absorption of water by the eye is governed by the same laws as the absorption of water by fibrin or gelatin.* The fresh eyes of sheep, pigs and cattle were employed shortly after their removal at the slaughter house. For the most part sheep eyes, carefully trimmed of adhering tags of muscle and fat, were used, but identical results can be obtained with the eyes of pigs or cattle. To avoid useless details only the conclusions from many series of experiments are given below, and these have been arranged in lettered paragraphs corresponding with similarly lettered ones in the sections on the swelling of fibrin and of gelatin. What has been said of fibrin and gelatin may thus be compared with what is said regarding the absorption of water by the eye.[1]

The amount of water absorption was measured by weighing the eyes at intervals and calculating the increase or decrease in weight in percentage of the original weight of the fresh (moist) eyes. The eyes were kept in lightly covered finger bowls containing enough of the various solutions to cover the eyes. 200 cc. are sufficient for sheep eyes, while the large cattle eyes demand

[1] For detailed weighings and figures, see MARTIN H. FISCHER: Pflüger's Arch., **125**, 396 (1908); ibid., **127**, 1 (1909).

300 cc. To make the weighings, the eyes were taken out of their solutions, carefully dried with soft filter paper and weighed as quickly as possible on balanced powder papers, such as are employed by pharmacists.

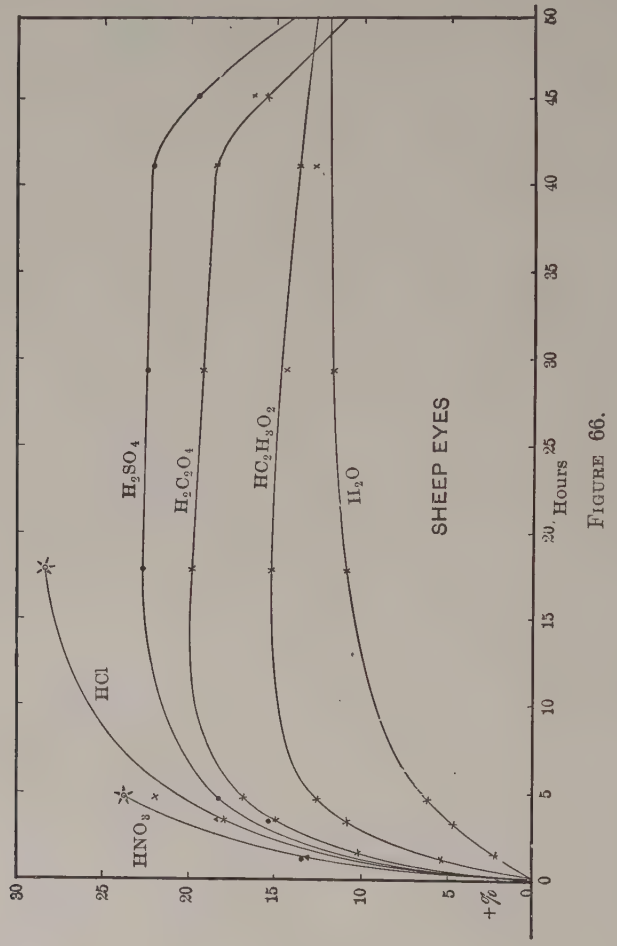


FIGURE 66.

The following conclusions are of importance in our discussion:

(*a*) An enucleated eye absorbs more water in the solution of any acid than in distilled water. When equinormal acids are compared they are found to be unequally effective in this regard. Fig. 66 shows graphically the results of a few such experiments

with n/110 acids. As easily apparent, the swelling in hydrochloric and nitric acids is sufficiently great to lead to a rupture of the eyeball—the sclera splits and allows the escape of the more fluid contents of the eye. Rupture of the eyeball is indicated in this figure and in all that follow by the five-cornered star at the end of the curves. Sulphuric, oxalic and acetic acids are

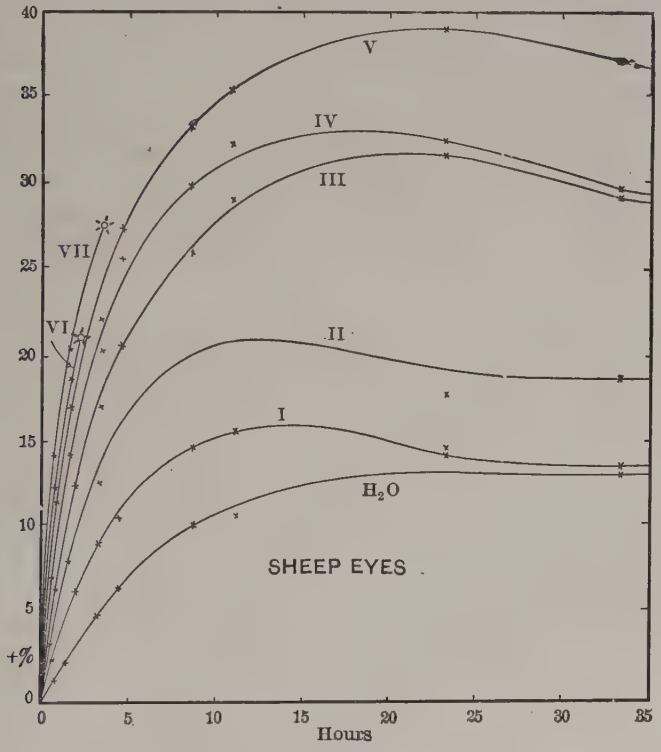


FIGURE 67.

all less potent in making eyes swell, for the absorption curves with these acids are decidedly lower, in the order named, than those for nitric and hydrochloric acids. In none of these does a rupture of the eyes occur at the concentrations employed. The curve obtained by immersion of an eye in pure water is introduced for comparison.

The amount that an eye swells in any acid solution is dependent on the concentration of the acid. This is illustrated in Fig. 67.

The curve for pure water is the lowermost one. The Roman numerals indicate progressively higher concentrations of hydrochloric acid. The solutions were made by adding, 2, 4, 6, 8, 12, 14 and 16 cc. of n/10 hydrochloric acid to enough water to make 220 cc. of solution. The acid solutions vary in consequence from n/1100 to n/137. A definite increase in the amount of swelling with every increase in concentration is readily discernible. In the highest concentrations the absorption of water is sufficiently great (and sufficiently rapid) to lead to rupture of the eye.

It is of extreme interest to note how low a concentration of acid brings about a decided absorption of water by the eye. The lowest concentration of hydrochloric acid in this series does not betray its acid character to the sense of taste; the second has a taste, but it cannot be recognized as sour. It requires imagination to recognize the acid taste even in the third concentration in which an eye becomes stony hard.

(*b*) Eyes swell more in the solution of an alkali than in pure water. While there is no question about this fact (see Fig. 68), the amount of difference in swelling between an eye in pure water and one in the solution of an alkali is not as great as that between an eye in water and one in an acid solution. The same explanation holds for this observation as was given for the difference in the amount of swelling of muscle in solutions of acids and alkalies. The eye after removal from the body spontaneously undergoes an acid change. This acid is neutralized by the alkali of the solution into which the eye is dropped, whereby a salt is formed, the presence of which inhibits the swelling of the eye in the alkaline solution. (See paragraph *d*, below.)

The different alkalies affect the swelling of the eyes to unequal degrees when equinormal solutions are compared, but the exact order in which they are effective is not yet definitely settled.

If the amounts are compared that an eye will swell in acid and in alkaline solutions having, respectively, the same H or OH concentration, it is found that an eye swells *less* in the solution of an alkali than in an equally concentrated acid. The curves marked HCl and KOH in Fig. 68 illustrate this, both solutions being n/110. The cause for this divergence from the behavior of fibrin was touched upon in the preceding paragraph.

(*c*) The presence of any salt reduces the amount that an eye

will swell in any acid or alkaline solution. Fig. 68 shows this as well as Figs. 69, 70, and 71. The effect of the pure acid or alkali (n/110, made by adding 20 cc. of their n/10 solutions to 200 cc. of water) is evidenced by the curves marked HCl and KOH in Fig. 68. When an eye is placed in solutions made by adding the

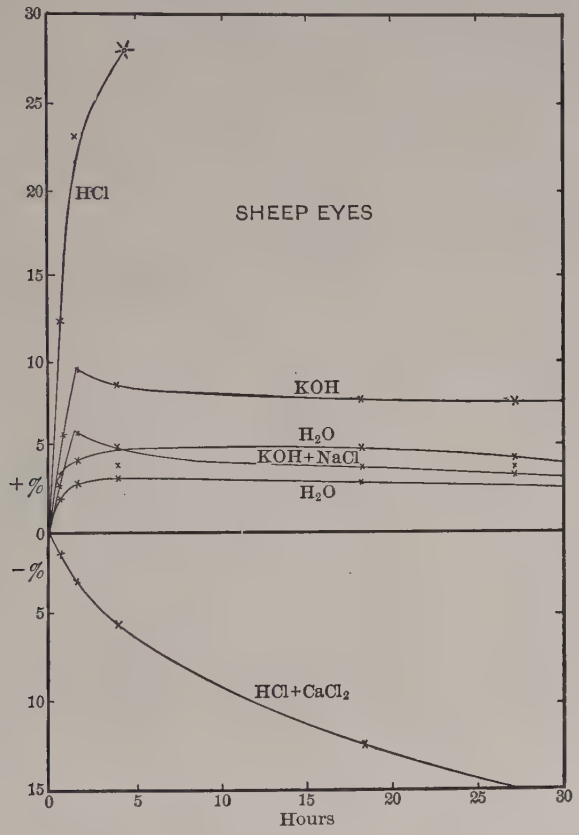


FIGURE 68.

same amounts of acid or alkali, respectively, to 200 cc. m/4 solutions of calcium chlorid or sodium chlorid, the curves marked $HCl+CaCl_2$ and KOH+NaCl are obtained. The curve of absorption in pure water is introduced as a control.

Fig. 69 shows that the higher the concentration of the added salt the less does an eye swell in an acid solution. The eye

bursts in the pure hydrochloric acid solution made by adding 20 cc. n/10 hydrochloric acid to 200 cc. of water. The remaining curves are self explanatory if it is stated that 20 cc. n/10 hydrochloric acid are added in each of these cases to 200 cc. of the appropriate solution of calcium nitrate.

(*d*) When the dehydrating effect of equimolar solutions of different salts is compared, they are found to be very unequally

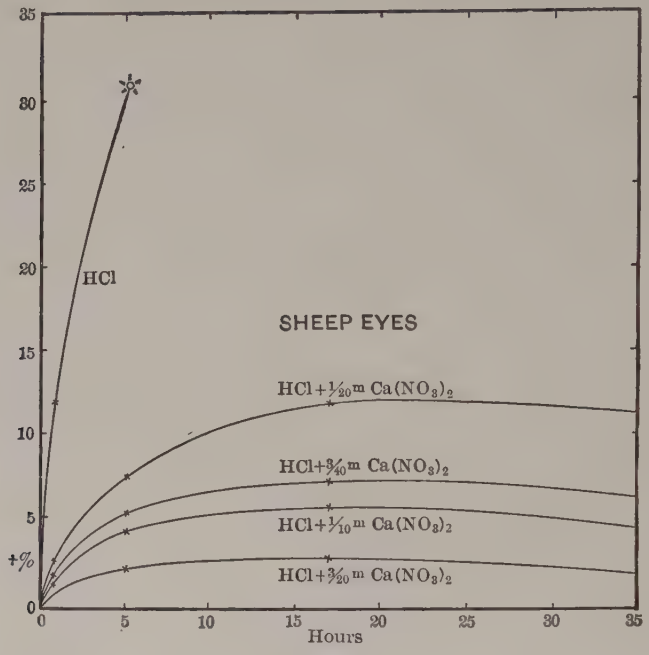


FIGURE 69.

effective in this regard. As in the case of fibrin or gelatin, the effect of any salt seems to be made up of the sum of the effects of its constituent radicals. Fig. 70 permits comparison of the action of different basic radicals. The eyes burst in both the pure hydrochloric acid solutions, but in none of those to which a salt had been added. The solutions containing salt were made by adding 20 cc. n/10 normal hydrochloric acid to 200 cc. m/6 solutions of the different chlorids. The bases arrange themselves in about the following order, in which that least effective in re-

ducing the amount of swelling in an acid solution is placed highest in the series, and first in each group:

1. Lithium, Ammonium, Potassium, Sodium.
2. Barium, Strontium, Magnesium, Calcium, Copper (ic).
3. Iron (ic).

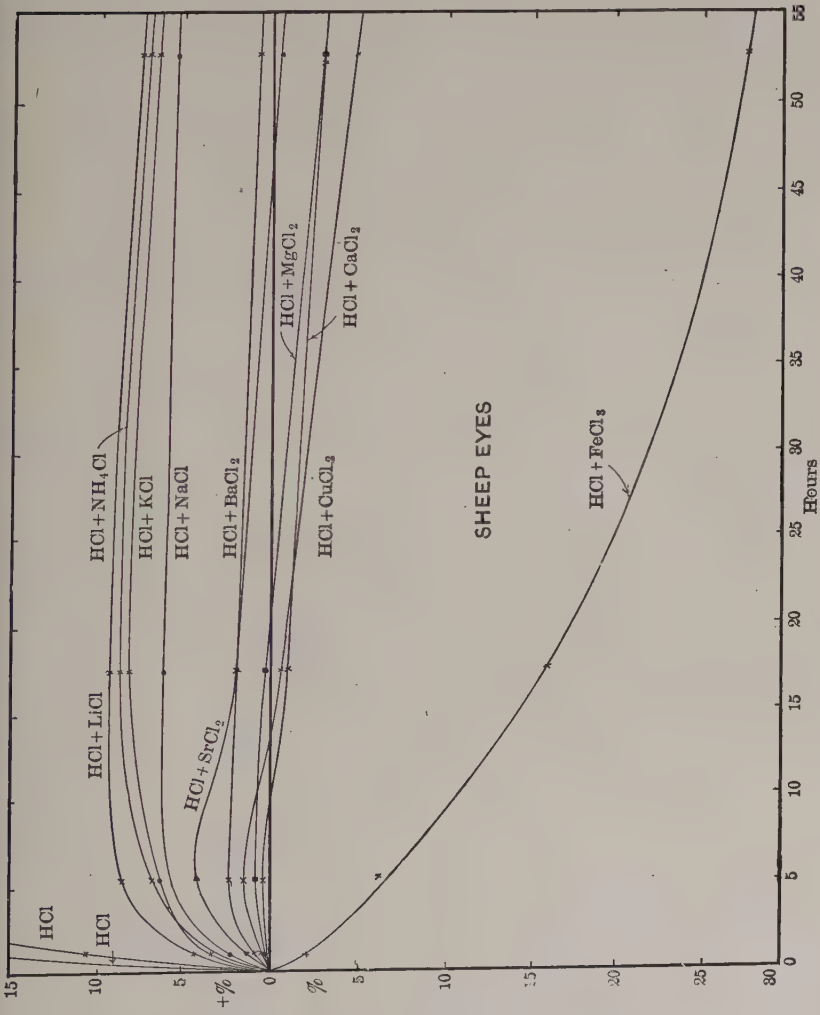


FIGURE 70.

We have small difficulty in discovering in this table the same grouping familiar to us from our discussion of the swelling of fibrin and gelatin.

In Fig. 71 are shown the effects of salts having different acid radicals. In each case 20 cc. n/10 hydrochloric acid are again added to 200 cc. of m/6 solution of the appropriate sodium salt.

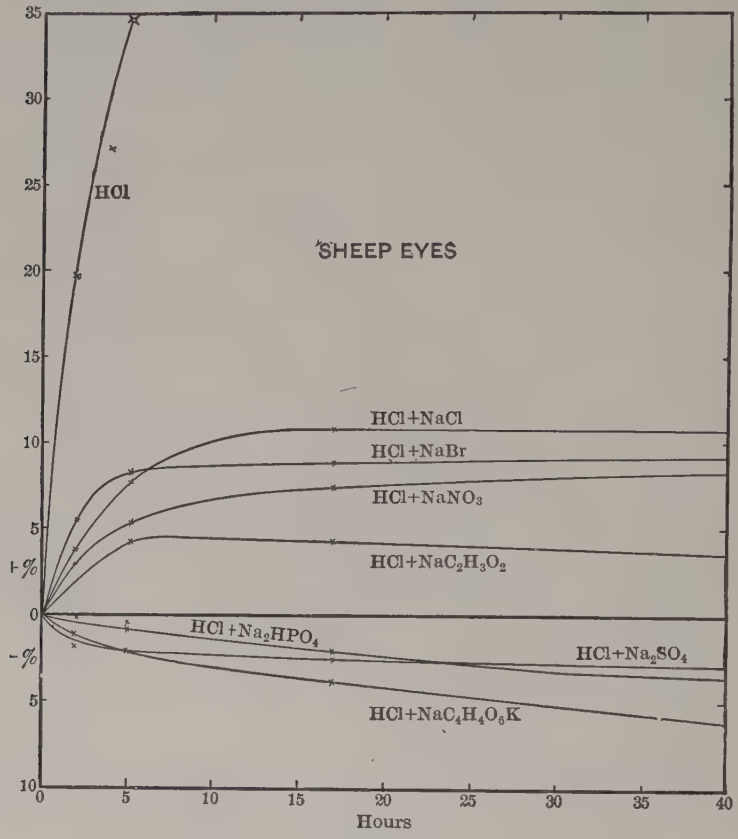


FIGURE 71.

Their order is as follows when that least effective in reducing the amount of swelling in an acid solution is placed first:

1. Chlorid, Bromid, Nitrate, Acetate.
2. Phosphate, Sulphate, Tartrate.

This table also is to all intents and purposes identical with that given in the discussion of water absorption by fibrin and gelatin.

(*e* and *f*) Non-electrolytes do not share with electrolytes their marked power of decreasing the absorption of water by the eye. Fig. 72 shows this better than many words. The curves lie very closely together, and in spite of the fact that the various non-electrolytes are present in amounts which are *osmotically* more than equivalent to the powerfully acting electrolytes (20 cc. n/10 HCl+200 cc. m/3 solution of the non-electrolyte), not one of the eyes has been kept from bursting.

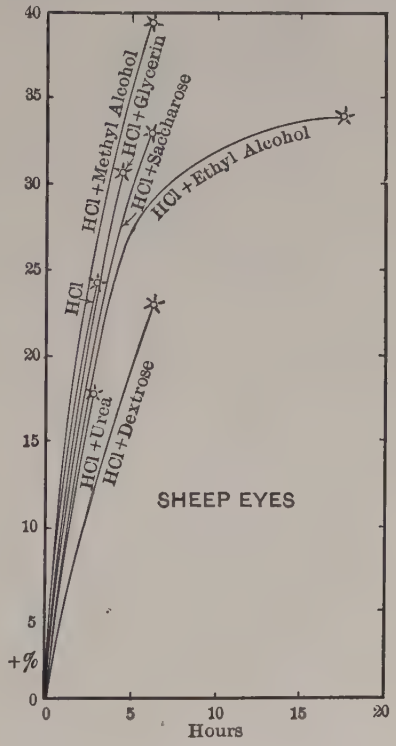


FIGURE 72.

(*g*) The absorption and secretion of water by the eye is largely a reversible process. This is indicated in Fig. 73. Curve A shows how an eye which has reached the bursting point in a pure hydrochloric acid solution suffers a prompt loss of water if taken out of this solution and transferred to an equally concentrated one containing calcium chlorid in addition. Curve B shows the reverse of this. An eye which has gained but little weight in pure water is transferred to a dilute hydrochloric acid solution. Immediately the absorption of water is hastened, and becomes so great that the eye bursts. The eye, also, suffers somewhat permanently from every condition through which it has passed. Once, for example, an eye has been in an acid containing a salt, it does not subsequently swell as much in a pure acid solution (in the time allowed in these experiments) as it would have done had it been placed here directly.

3. The Analogy between the Absorption of Water by Certain Protein Colloids and by Nervous Tissue

The complete analogy between the absorption of water by certain protein colloids and by muscle and the eye as outlined in

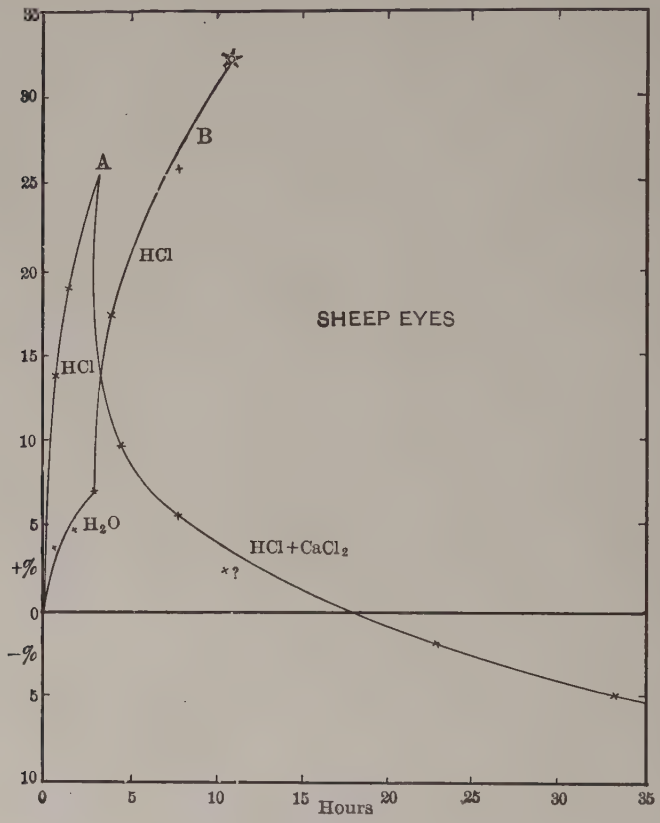


FIGURE 73.

the preceding sections seemed to me to justify the conclusion that the colloids and their state are chiefly if not entirely responsible for the amount of water held by any cell, tissue or organ under different circumstances. Since this conclusion was first voiced, it has found generous acceptance and support from a

number of investigators.[1] But it has also met with opposition. Here we must consider the objections of J. BAUER,[2] who believes that in nervous tissues water absorption is not, in the main, a function of the protein colloids found in them. Before pointing out the obvious errors in BAUER's experiments and conclusions, let us first look at the following experiments made by MARIAN O. HOOKER[3] and me, which, contrary to BAUER's view, show that *the absorption and secretion of water by nervous tissues (brain and spinal cord) is entirely analogous to the absorption and secretion of water by such protein colloids as fibrin or gelatin.*[4]

To obtain perfectly fresh nervous tissue in as unchanged a condition as possible, we used normal rabbits which had been on a generous mixed diet, killed them by a gentle blow behind the ears and then rapidly dissected out the brain and spinal cord. The dura and arachnoid membranes were removed and the pia was peeled off as well as possible. The nervous tissues were cut into pieces of approximately the same size. In each series of experiments the pieces used were always taken from the same animal. This is necessary, for comparatively trivial things influence the initial state of the nervous tissue. If an animal is chased about its cage just before being used, or is ill, its nervous tissues show a different capacity for absorbing water, due, in the main, we think, to differences in their initial acid content, than when such things have not happened. In the same way the stale tissues from an animal dead some hours or days show different absorption curves (because of a higher initial acid content) than fresh ones.

After weighing, the pieces of tissue were introduced into the different solutions. At various times they were taken out, re-

[1] See for example: I. TRAUBE: Pflüger's Arch., **140**, 109 (1911); K. GEDROIZ: Russ. Journ. f. exp. Landwirtsch., **11**, 66 (1910). E. PŘZIBRAM: Kolloidchem. Beihefte, **2**, 1 (1910). H. KLOSE: Arch. f. Kinderheilk., **55**, 43 (1910). H. BECHHOLD: Colloids in Biology and Medicine, translated by BULLOWA, New York (1919). H. KLOSE and H. VOIGT: Beitr. z. klin. Chirurgie, 69 (1910). O. PÖTZL and A. SCHÜLLER: Zeitschr. f. d. ges. Neurologie, 3 (1910). RUDOLF ARNOLD: Kolloidchem. Beihefte, **5**, 411 (1914).

[2] J. BAUER: Arb. a. d. neurol. Inst. d. Wiener Univ., **19**, 87 (1911); Kolloid-Zeitschrift, **9**, 112 (1911).

[3] MARIAN O. HOOKER and MARTIN H. FISCHER: Kolloid-Zeitschr., **10**, 283 (1912), where detailed weighings may be found.

[4] For further evidence in this direction and independent criticism of BAUER's conclusions see RAPHAEL ED. LIESEGANG: Ergebnisse d. Neurol. u. Psych., **2**, 157 (1912).

weighed and the increase or loss calculated in percentage of their original weight. The results are shown in the accompanying curves, which were made by plotting time on the horizontal and changes in weight on the vertical. As they are all drawn to the same scale they may be compared directly with each other.

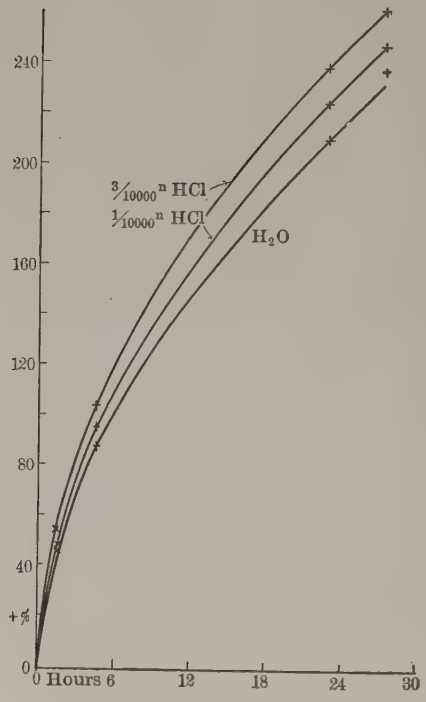


FIGURE 74.

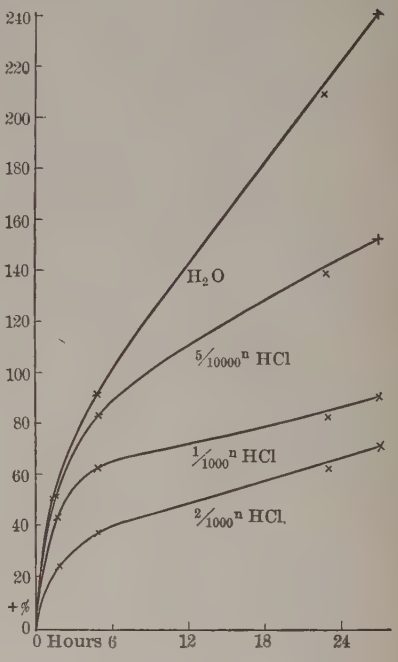


FIGURE 75.

To indicate their complete analogy the following paragraphs on the absorption of water by nervous tissue are lettered to correspond with the similarly lettered paragraphs in the sections on fibrin and gelatin.

(*a* and *b*) When nervous tissue (brain) is placed in distilled water it takes this up (gains in weight). We shall at once interpret this by saying that after removal from the body the tissue develops acid and this increases the capacity of the brain colloids for holding water. If the brain is placed in a dilute acid

instead of in water it swells decidedly more. With every increase in the concentration of the acid the amount of water absorption is increased. These facts are brought out in the curves of Fig. 74. But the increased swelling with increase in concentration of acid continues only up to a certain point, when every further addition of acid only reduces the amount of water absorbed. This is shown in Fig. 75. The curves of Figs. 74 and 75 are based respectively upon the experimental data contained in Tables LXVII and LXVIII:

TABLE LXVII

ADULT RABBIT BRAIN

Hours in the Solution.	100 cc. H_2O	100 cc. 1/10000 n HCl	100 cc. 3/10000 n HCl
	%	%	%
0	1.228 (0)	1.142 (0)	0.865 (0)
1.20	1.825 (+ 49)	1.682 (+ 47)	1.346 (+ 55)
4.20	2.336 (+ 90)	2.247 (+ 97)	1.765 (+104)
22.35	3.775 (+208)	3.850 (+237)	1.775 (+221)
27.00	4.185 (+240)	3.950 (+246)	3.110 (+260)

TABLE LXVIII

ADULT RABBIT BRAIN

Hours in the Solution.	100 cc. 2/1000 n HCl	100 cc. 1/1000 n HCl	100 cc. 5/10000 n HCl	100 cc. H_2O
	%	%	%	%
0	0.630(0)	0.650 (0)	0.663 (0)	1.228 (0)
1.20	0.785 (+25)	0.926 (+43)	1.005 (+ 52)	1.825 (+ 49)
4.20	0.866 (+38)	1.066 (+64)	1.210 (+ 83)	2.336 (+ 90)
22.40	1.030 (+64)	1.205 (+85)	1.575 (+138)	3.775 (+208)
27.00	1.090 (+73)	1.240 (+91)	1.680 (+153)	4.185 (+240)

(*c*) The amount of acid developed in nervous tissue after removal from the body is so near that leading to a maximum of water absorption that none needs to be added from the outside in our further experiments. If we place the pieces of tissue in pure solutions of various kinds we shall in reality be observing the effect of these plus that of a certain amount of acid (produced by the tissue itself).

Fig. 76 (as well as Figs. 77, 78, 79, 80, 81 and 82) shows that the addition of any electrolyte to the (acid) solution in which

brain tissue is swelling reduces the amount of water absorbed. This reduction is the greater the higher the concentration of the added electrolyte. Fig. 77 shows the same to be true for spinal

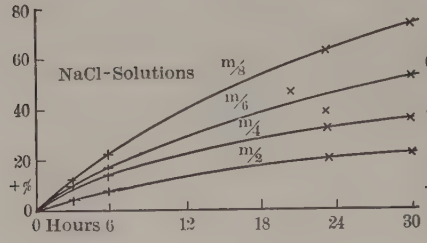


FIGURE 76.

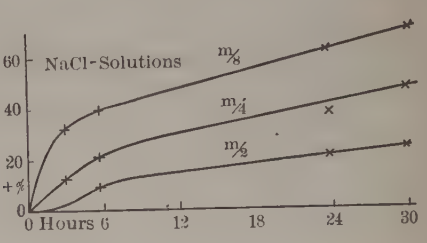


FIGURE 77.

cord. The experimental data contained in Tables LXIX and LXX form the basis of Figs. 76 and 77.

TABLE LXIX

YOUNG RABBIT BRAIN

Hours in the Solution.	120 cc. m/2 NaCl	120 cc. m/4 NaCl	120 cc. m/6 NaCl	120 cc. m/8 NaCl
	%	%	%	%
0	0.808 (0)	0.860 (0)	0.915 (0)	0.982 (0)
2.45	0.822 (+ 2)	0.945 (+10)	1.000 (+ 9)	1.087 (+11)
5.45	0.855 (+ 6)	0.980 (+14)	1.075 (+17)	1.212 (+23)
23.15	0.977 (+21)	1.141 (+33)	1.267 (+38)	1.605 (+63)
29.25	1.005 (+24)	1.178 (+37)	1.410 (+56)	1.715 (+75)

TABLE LXX

SPINAL CORD OF YOUNG RABBIT

(Same Animal as in Table LXIX)

Hours in the Solution.	120 cc. m/2 NaCl	120 cc. m/4 NaCl	120 cc. m/8 NaCl
	%	%	%
0	0.072 (0)	0.081 (0)	0.142 (0)
3.00	0.057 (− 2)	0.092 (+13)	0.192 (+35)
5.30	0.080 (+11)	0.100 (+23)	0.200 (+41)
23.20	0.086 (+20)	0.112 (+38)	0.230 (+62)
29.25	0.090 (+26)	0.120 (+48)	0.242 (+70)

(*d*) Equimolar concentrations of different salts reduce in very unequal degree the swelling of nervous tissue (in any acid solution).

In Figs. 78, 79 and 80 some salts are compared having the same basic, but different acid radicals. In Fig. 78 the sodium

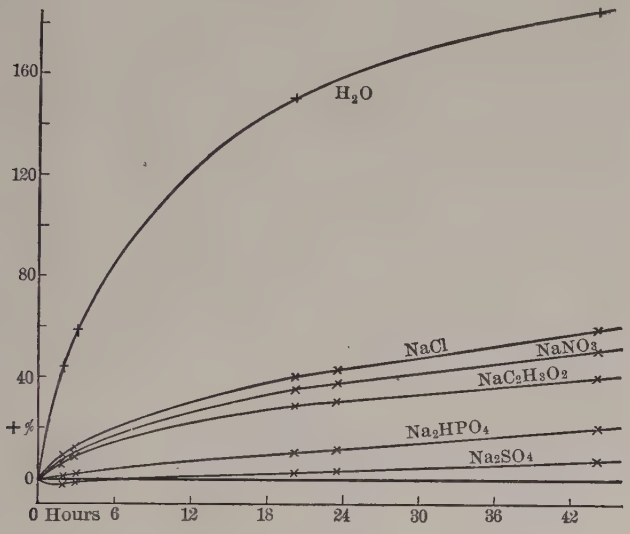


FIGURE 78.

salts are seen to arrange themselves in the following familiar order when that least effective in preventing swelling is given first:

Chlorid, Nitrate, Acetate, Phosphate, Sulphate.

In Fig. 79 the potassium salts assume the following order:

Chlorid, Acetate, Citrate.

Or in Fig. 80:

Bromid, Iodid, Sulphocyanate, Nitrate.

The dehydrating action of salts having the same acid radical but different bases is compared in Figs. 81 and 82. In the

chlorid series when the salt least effective in inhibiting swelling is given first, we see the order:

Ammonium, Sodium, Potassium, Strontium, Barium, Magnesium, Copper,

or in the nitrate series similarly arranged:

Ammonium, Potassium, Sodium, Strontium, Magnesium, Barium, Calcium, Iron.

The dehydrating action of these salts on nervous tissue is practically identical, therefore, with their dehydrating action on fibrin or gelatin.

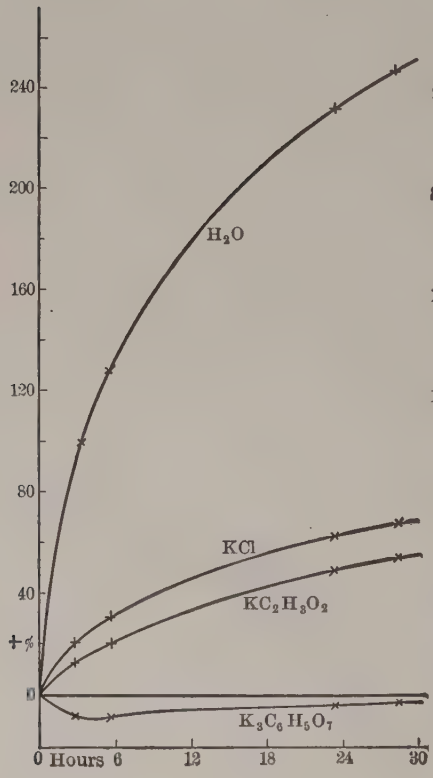


FIGURE 79.

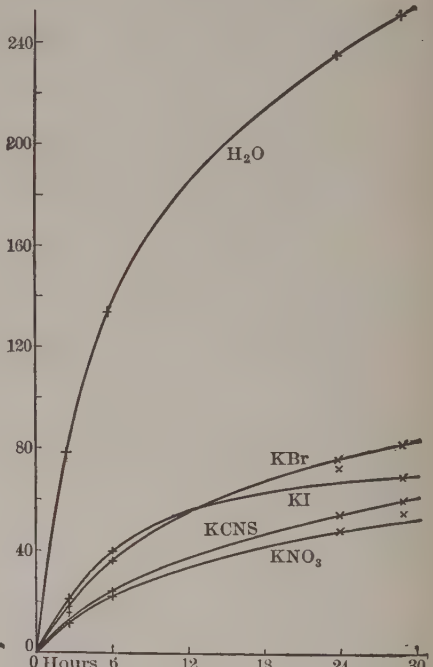


FIGURE 80.

Figs. 78, 79, 80, 81 and 82 are based respectively upon the data contained in Tables LXXI, LXXII, LXXIII, LXXIV,

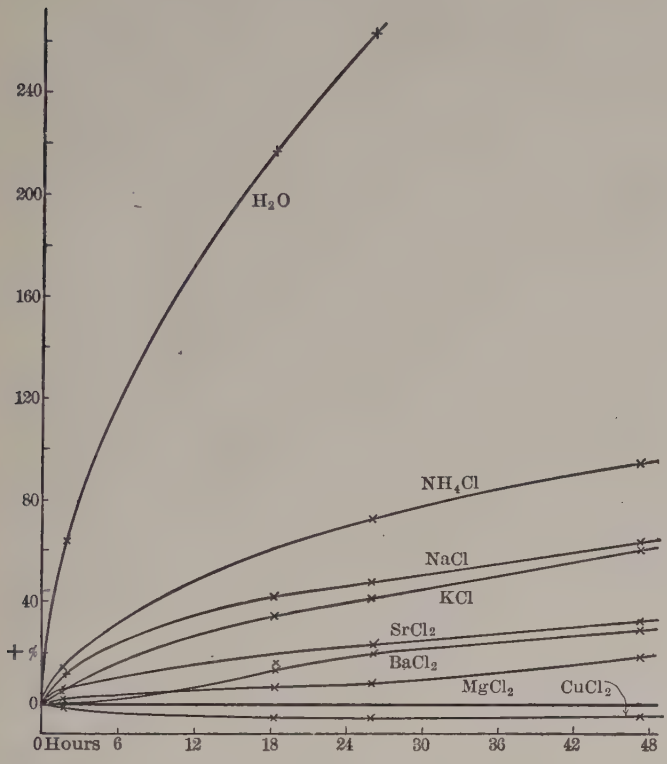


FIGURE 81.

TABLE LXXI

BRAIN OF RABBIT

Hours in the Solution.	100 cc. m/6 Na_2SO_4	100 cc. m/6 Na_2HPO_4	100 cc. m/6 $NaC_2H_3O_2$	100 cc. m/6 $NaNO_3$	100 cc. m/6 NaCl	100 cc. H_2O
	%	%	%	%	%	%
0	0.766 (0)	0.751 (0)	1.220 (0)	1.200 (0)	0.752 (0)	1.120 (0)
2.00	0.766 (0)	0.741 (− 1)	1.251 (+ 3)	1.291 (+ 8)	0.799 (+ 3)	1.595 (+ 42)
3.00	0.752 (− 2)	0.755 (+ 1)	1.270 (+ 4)	1.310 (+10)	0.837 (+11)	1.780 (+ 59)
20.15	0.771 (+ 1)	0.827 (+10)	1.565 (+29)	1.639 (+36)	1.063 (+41)	2.821 (+152)
24.10	0.781 (+ 2)	0.826 (+10)	1.580 (+30)	1.640 (+37)	1.087 (+44)	2.814 (+151)
44.35	0.820 (+ 7)	0.910 (+21)	1.710 (+40)	1.825 (+52)	1.202 (+59)	3.195 (+185)
68.15	0.855 (+10)	0.966 (+28)	1.825 (+50)	1.975 (+65)	1.265 (+68)	3.223 (+188)

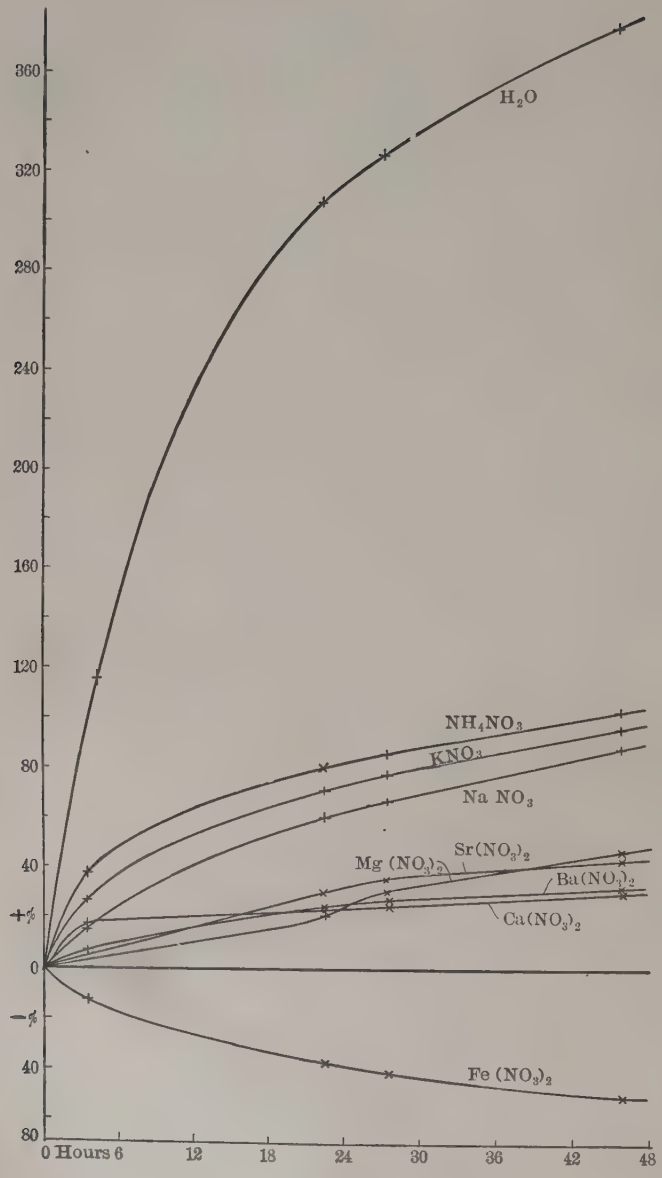

360
320
280
240
200
160
120
80
40
+%
0
−%
40
80
0 Hours 6
12
18
24
30
36
42
48
H_2O
NH_4NO_3
KNO_3
$Na\ NO_3$
$Mg\ (NO_3)_2$
$Sr(NO_3)_2$
$Ba(NO_3)_2$
$Ca(NO_3)_2$
$Fe\ (NO_3)_2$

FIGURE 82.

TABLE LXXII

Brain of Rabbit

Hours in the Solution.	120 cc. m/6 Calcium citrate	120 cc. m/6 Calcium acetate	120 cc. m/6 Calcium chlorid	120 cc. H_2O
	%	%	%	%
0	1.086(0)	0.685(0)	1.072(0)	0.623 (0)
2.30	0.992 (−8)	0.770(+13)	1.308(+ 22)	1.100 (+ 78)
5.35	0.995 (−8)	0.815(+20)	1.410(+ 31)	1.450 (+133)
23.50	1.060 (−2)	1.033(+51)	1.753(+ 63)	2.075 (+233)
28.25	1.060 (−2)	1.050(+54)	1.795(+ 68)	2.165 (+247)
47.30	1.120 (+3)	1.160 (+70)	2.005(+ 87)	1.858[1](+198)
71.20	1.185 (+9)	1.245 (+82)	2.170(+102)	1.690[1](+171)

[1] Going into solution.

TABLE LXXIII

Brain of Rabbit

Hours in the solution.	120 cc. m/6 KNO_3	120 cc. m/6 KCNS	120 cc. m/6 KI	120 cc. m/6 KBr	120 cc. H_2O
	%	%	%	%	%
0	1.241 (0)	1.105 (0)	0.712 (0)	0.773 (0)	0.623 (0)
2.30	1.388 (+12)	1.286 (+17)	0.863 (+21)	0.916 (+ 18)	1.100 (+ 78)
5.35	1.510 (+22)	1.363 (+23)	0.978 (+37)	1.047 (+ 35)	1.450 (+133)
23.30	1.822 (+47)	1.693 (+53)	1.235 (+73)	1.350 (+ 74)	2.075 (+233)
28.25	1.973 (+59)	1.713 (+55)	1.200 (+68)	1.395 (+ 80)	2.165 (+247)
47.30	2.125 (+71)	1.867 (+69)	1.285 (+80)	1.475 (+ 91)	1.858[1] (+198)
71.20	2.245 (+81)	2.070 (+88)	1.375 (+93)	1.590 (+106)	1.690[1] (+171)

[1] Going into solution.

TABLE LXXIV

Adult Rabbit Brain

Hours in the Solution.	120 cc. m/6 $CuCl_2$	120 cc. m/6 $MgCl_2$	120 cc. m/6 $BaCl_2$	120 cc. m/6 $SrCl_2$
	%	%	%	%
0	0.791 (0)	0.685 (0)	1.010 (0)	0.878 (0)
1.30	0.775 (−2)	0.692 (+ 1)	1.010 (0)	0.910 (+ 4)
18.15	0.753 (−5)	0.723 (+ 6)	1.155 (+14)	1.005 (+14)
26.00	0.747 (−6)	0.730 (+ 7)	1.217 (+20)	1.083 (+23)
47.15	0.749 (−5)	0.810 (+18)	1.297 (+28)	1.158 (+32)
67.60	0.765 (−3)	0.887 (+30)	1.450 (+43)	1.230 (+40)

Hours in the Solution.	120 cc. m/6 KCl	120 cc. m/6 NaCl	120 cc. m/6 NH_4Cl	120 cc. H_2O.
	%	%	%	%
0	0.998 (0)	0.558 (0)	0.788 (0)	0.526 (0)
1.30	1.023 (+ 3)	0.625 (+12)	0.883 (+ 12)	0.875 (+ 63)
18.15	1.337 (+34)	0.793 (+42)	1.385 (+ 76)	1.708 (+213)
26.00	1.430 (+43)	0.815 (+46)	1.365 (+ 73)	1.945 (+263)
47.15	1.600 (+60)	0.910 (+63)	1.530 (+ 94)	1.872[1] (+250)
67.60	1.832 (+84)	1.017 (+82)	1.710 (+117)	1.642[1] (+206)

[1] Going into solution.

TABLE LXXV

ADULT RABBIT BRAIN

Hours in the solution.	120 cc. m/6 $Fe(NO_3)_3$	120 cc. m/6 $Ca(NO_3)_2$	120 cc. m/6 $Ba(NO_3)_2$	120 cc. m/6 $Sr(NO_3)_2$	120 cc. m/6 $Mg(NO_3)_2$
	%	%	%	%	%
0	0.575 (0)	0.785 (0)	0.535(0)	0.820 (0)	0.742 (0)
3.45	0.495 (−14)	0.842 (+ 8)	0.575 (+ 7)	0.867 (+ 5)	0.765 (+ 3)
22.45	0.362 (−37)	0.955 (+22)	0.660 (+23)	1.035 (+26)	0.887 (+20)
27.45	0.332 (−42)	0.960 (+22)	0.673 (+26)	1.105 (+35)	0.965 (+30)
46.15	0.278 (−51)	1.020 (+30)	0.705 (+31)	1.158 (+41)	1.072 (+45)
70.15	0.240 (−58)	1.060 (+35)	0.763 (+43)	1.283 (+58)	1.215 (+64)

Hours in the solution.	120 cc. m/6 $NaNO_3$	120 cc. m/6 KNO_3	120 cc. m/6 NH_4NO_3	120 cc. H_2O
	%	%	%	%
0	0.610 (0)	0.758(0)	0.828 (0)	0.370 (0)
3.45	0.708 (+16)	0.975 (+ 29)	1.155 (+ 39)	0.810 (+117)
22.45	0.970 (+60)	1.288 (+ 70)	1.465 (+ 79)	1.505 (+306)
27.45	1.005 (+65)	1.350 (+ 75)	1.525 (+ 84)	1.560 (+322)
46.15	1.135 (+86)	1.485 (+ 95)	1.742 (+110)	1.745 (+372)
70.15	1.205 (+97)	1.565 (+105)	1.732[1] (+109)	1.910 (+420)

[1] Going into solution.

(*e* and *f*) At the same concentration the non-electrolytes are far less powerful in reducing the swelling of nervous tissue (in an acid medium) than the electrolytes. Fig. 83 and Table LXXVI show this. Even though the three alcohols were present in a concentration osmotically equal to or higher than that of the electrolytes used in the experiments previously described, a decrease in the amount of swelling is either not evident at all or but slight. As both the figure and the table indicate, urea seems actually to favor the absorption of water.

TABLE LXXVI

ADULT RABBIT BRAIN

Hours in the solution.	120 cc. m/3 Glycerin	120 cc. m/3 Urea	120 cc. H_2O	120 cc. m/3 Methyl Alcohol	120 cc. m/3 Ethyl Alcohol
	%	%	%	%	%
0	0.832(0)	0.828 (0)	1.227 (0)	0.905 (0)	0.978 (0)
4.00	1.153 (+ 39)	1.560 (+ 81)	2.200 (+ 79)	1.572 (+ 73)	1.782 (+ 82)
23.45	1.902 (+130)	2.347 (+183)	3.475 (+183)	2.605 (+189)	2.982 (+205)
28.00	2.188 (+163)	2.315[1] (+179)	3.840 (+213)	2.830 (+213)	3.252 (+232)
46.30	2.595 (+210)	2.510 (+203)	4.345 (+255)	3.200 (+253)	3.695 (+277)
70.30	2.904 (+249)	.....	4.280[1] (+248)	3.288 (+263)	3.935 (+303)

[1] Going into solution.

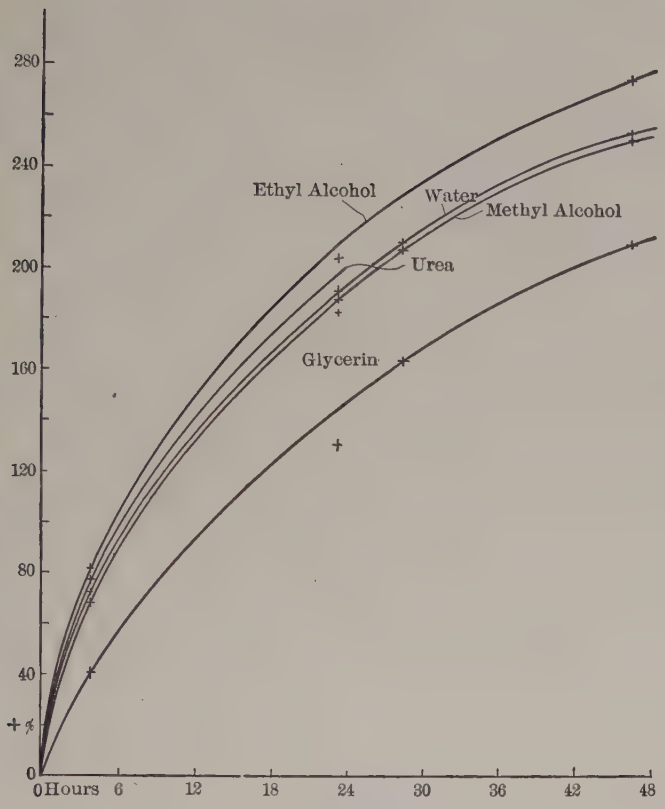


FIGURE 83.

TABLE LXXVII

ADULT RABBIT BRAIN

Hours in the solution.	120 cc. H_2O	120 cc. m/6 NaCl	120 cc. m/6 NaCl	120 cc. H_2O
	%	%	%	%
0	1.150 (0)	.....	1.100 (0)	
2.25	2.030 (+76)	.....	1.260 (+15)	
3.25	2.050 (+78)	.....	1.305 (+19)	
	Transferred	.....	Transferred	
4.20	.....	1.670 (+45)	.....	1.480 (+ 35)
6.00	.....	1.630 (+41)	.....	1.760 (+ 60)
24.00	.....	1.845 (+59)	.....	2.830 (+157)
		Transferred	.....	Transferred
25.45	1.970 (+ 71)	.....	2.075 (+89)	
29.35	2.090 (+ 82)	.....	1.920 (+75)	
47.45	2.467 (+114)	.....	1.700 (+55)	

(*g*) The absorption and secretion of water by nervous tissue represents in large part a reversible process. This is brought out

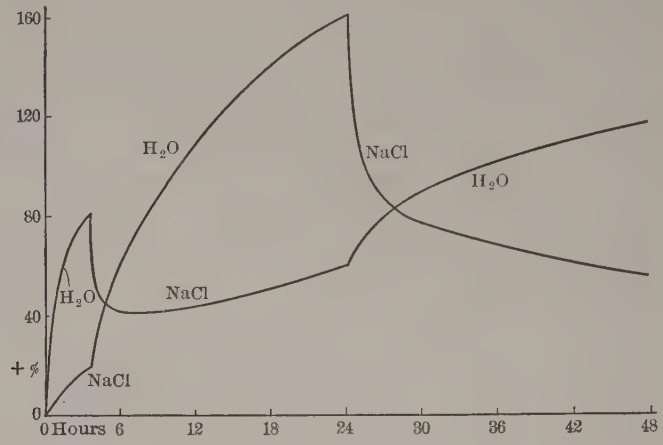


FIGURE 84.

in Figs. 84 and 85 and Tables LXXVII and LXXVIII, upon which these drawings are based. If nervous tissue is placed in a dilute

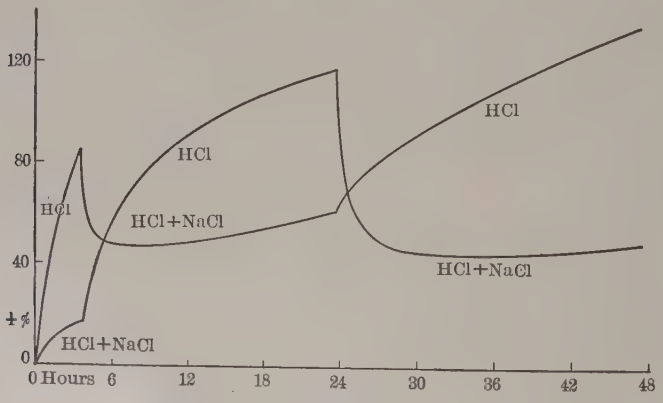


FIGURE 85.

acid or in water (which amounts to placing it in a dilute acid) it swells. If, after any desired degree of swelling has been attained, the tissue is transferred to an equally concentrated

acid containing a salt, the swelling ceases and a loss of water begins. If now the tissue is returned to the pure acid or to water, rapid absorption again occurs. A reverse set of facts and curves is obtained if the tissue is first placed in acid plus salt, then in pure acid and then again in acid plus salt, as is also evident in Figs. 84 and 85.

TABLE LXXVIII

Adult Rabbit Brain

Hours in the solution.	120 cc. m/6 NaCl +0.2 cc. n/10 HCl	120 cc. H_2O +0.2 cc. n/10 HCl	120 cc. H_2O +0.2 cc. n/10 HCl	120 cc. m/6 NaCl +0.2 cc. n/10 HCl
	%	%	%	%
0	1.517 (0)	.....	1.280(0)	
2.30	1.730 (14+)	.....	2.180 (+70)	
3.30	1.765 (16+)	.....	2.370 (+85)	
	Transferred	.....	Transferred	
4.20	.....	2.015(+ 33)	.....	1.950 (+52)
6.00	.....	2.370(+ 56)	.....	1.890 (+48)
23.45	.....	3.295 (+117)	.....	2.070 (+62)
		Transferred	.....	Transferred
25.45	2.333 (+54)	.....	2.217 (+ 74)	
29.45	2.205 (+45)	.....	2.430 (+ 90)	
47.45	2.247 (+48)	.....	2.993 (+134)	

These experiments dispose, we think, of Bauer's objections which have been taken up in detail elsewhere.[1] His conclusion that acids only dehydrate nervous tissue was reached because he chose his acid concentrations too high (beyond those optimal for brain swelling), and because he worked with stale tissues (six to twenty-four hours old) so rich in postmortem acids that a further addition of acid from the outside could only decrease their power of swelling.

In concluding these paragraphs, attention may be directed to Fig. 86, which shows how enormously brain tissue can swell. The figure shows the two halves of a young rabbit's brain and spinal cord split longitudinally. The half marked *a* was carefully protected from evaporation, that marked *b* was kept in a n/10,000 lactic acid solution. At the end of twenty-four hours

[1] Marian O. Hooker and Martin H. Fischer: Kolloid-Zeitschr., **10**, 292 (1912).

it had gained twice its original weight (200 per cent) in water. Since fatal brain œdemas show an increase in weight of less than

FIGURE 86.

10 per cent it is readily apparent how easily such may be accounted for on the basis of colloid swelling.

IV

THE BIOLOGICAL SIGNIFICANCE OF THE ANALOGY BETWEEN THE ABSORPTION OF WATER BY CERTAIN PROTEIN COLLOIDS AND THE ABSORPTION OF WATER BY DIFFERENT TISSUES

1. Introductory Remarks

The complete analogy from both a quantitative and a qualitative point of view between the absorption of water by certain colloids and by widely differing types of tissues seems to me to warrant the conclusion that *the colloids and their state are the main factors concerned in determining the amount of water held by a cell, a tissue, an organ or a whole individual under different physiological or pathological circumstances.*

That they might be of some importance in this regard has occurred to several observers, but careful study of their papers shows that for the most part they dismissed the thought with little more than mere reference to its possible rôle, or the added remark that its significance in the general problem could not be great. Interestingly enough W. Pfeffer,[1] who worked so earnestly for the establishment of the importance of osmotic pressure as the great regulator of the water content of cells, seems to have been the first to regard the pressure of swelling (Quellungsdruck) as of use in explaining various exceptions to the laws of osmotic pressure as studied in botanical material. Later Franz Hofmeister[2] developed the same idea experimentally in his now classic and fundamental discussions of the biological significance of the colloid state. Durig[3] expressed the belief that studies on the swelling of colloids might help to explain the exceptions to the laws of osmotic pressure noted in his experiments on the absorption of water by frogs in various solutions. Rudolf Höber[4] and E.

[1] W. Pfeffer: Pflanzen Physiologie, Leipzig, **1**, 116 (1897); see also the first edition of 1881, **1**, 26 to 29.

[2] F. Hofmeister: Arch. f. exp. Path. u. Pharm., **28**, 210 (1891).

[3] Durig: Pflüger's Arch., **85**, 401 (1901).

[4] R. Höber: Physikalische Chemie d. Zelle u. d. Gewebe, 2d Ed., 61, 62 and 70, Leipzig, (1906); Koranyi-Richter's Physikalische Chemie u. Medizin, **1**, 294, Leipzig (1907); Höber's latest writings condemn the colloid-chemical view of water absorption and my support of it entirely. Biol. Zentralbl., **31**, 575 (1911).

OVERTON[1] also considered the subject. Both, however, laid greatest stress on the osmotic conception of water absorption by cells, especially as modified by the belief that the osmotic membrane about cells is fat-like (lipoid) in character. The rôle of the colloids is by both these authors not considered the fundamental factor in absorption, but is simply pointed to as one useful in explaining some of the many exceptions found to exist between the actual and the theoretical behavior of cells when these are regarded as osmotic systems. Much the same position is taken by H. J. HAMBURGER.[2] The colloids as a factor in the regulation of the water content of organs have also been discussed by WOLFGANG OSTWALD[3] and WOLFGANG PAULI.[4] PAULI pointed out that the swelling of red and white blood corpuscles in solutions of a dilute acid is not unlike the swelling of certain colloids, but in his discussion of the swelling of muscle he decided against this being essentially a colloid phenomenon because the analogy between the swelling of muscle and the swelling of certain colloids was not sufficiently close. His unfortunate conclusion was due to the fact that he compared the careful observations at hand on the swelling of gelatin with a group of inadequate observations on the swelling of muscle.

The experiments just detailed on the analogy between the absorption of water by protein colloids and by muscle, eyes and nervous tissue constitute, so far as I know, the first attempt to establish *experimentally* not only the quantitative, but the qualitative importance of the colloids of the tissues in determining the amount of water held by them. From a quantitative standpoint, we found that certain (hydrophilic) protein colloids are readily able to absorb amounts of water which are larger than any we have to account for in protoplasm, and from a qualitative standpoint we found that the behavior of protoplasm toward various external conditions, so far as its water content is concerned, is no different from the behavior of some simple colloids toward the same external conditions.

The individual cell which we call an ameba is, in its pond

[1] E. OVERTON: Nagel's Handbuch der Physiologie, **2**, 744, Braunschweig (1906), where references to his earlier papers will be found.

[2] H. J. HAMBURGER: Osmotischer Druck und Ionenlehre. See especially **3**, 4 to 33, 50 to 54 and 108 to 144, Wiesbaden (1902 to 1904).

[3] WOLFGANG OSTWALD: Personal Communication.

[4] WOLFGANG PAULI: Ergebnisse der Physiologie, **6**, 126 to 129 (1907).

water, like a fibrin flake floating in a solution of some kind. Let us add acid to the medium in which the ameba lives and it swells as does the fibrin flake; or let us add salt, and both shrink. The aggregate of cells which we call tissues, or organs, behave similarly. Only for the words pond water we need to substitute blood or lymph, for this is the medium in which the cells of our body lie and from which they absorb as does the ameba an amount of water which is determined by the nature and the state of the colloids found in the cells. But to accept the absorption of water by colloids as the most important factor in the absorption of water by the tissues is to arraign all the explanations which have thus far been given for the normal and abnormal variations in the amount of water held by protoplasm. We must, in consequence, study them for a moment in order to see if the conception which we have introduced of the variable capacity of the colloids for holding water merely adds to the forces already considered as active in protoplasm or whether the acceptance of the ideas here advanced necessitates a revision of our former beliefs.

We can at once dismiss as purposeless all "explanations" which are of a "vitalistic," "neovitalistic" or "physiological" character—they are mere salves for the undiagnosed sore. Of clearly defined physical or physico-chemical explanations, two have assumed special prominence. The first of these originated with the plant physiologists and has been widely adopted by the animal physiologists. We may call it for short the osmotic theory of water absorption, and with it consider that modification of it which has come with the belief that the semipermeable membrane assumed to surround cells is fat-like (lipoid) in character. The second was born of the pathologists, and may be called the pressure theory. As we need to discuss it in detail later we dismiss it temporarily and here consider only the osmotic theory.

2. Criticism of the Osmotic Theory of Water Absorption by Protoplasm

The osmotic theory has until rather recently represented the best attempt to analyze in physico-chemical terms the processes of absorption and secretion by living cells. As espoused to-day by different workers, it has suffered strange and self-

contradictory modifications from the original form in which it was put forward by Wilhelm Pfeffer and Hugo de Vries, but the work of these two continues the foundation upon which the moderns have built, and if we would not get lost in terminology we must consider their work first.

In order to account for the "turgor" (that is, the water content) of plant cells Pfeffer and de Vries held them to be surrounded by "osmotic" "membranes" of such character that while they gave passage to water they did not permit substances dissolved in this water to go through. On such basis they explained the swelling of plant cells in water or dilute solutions or their shrinkage in concentrated ones by saying that in the former water is sucked into the cell, while in the latter it is sucked out. The movement of water into or out of the cell occurs until the (osmotic) concentration of the dissolved substances is the same on both sides of the membrane postulated to exist about the cells. But, in order to permit the water to move, this membrane must be impermeable to the dissolved substances (otherwise, of course, they would simply move from a region of higher concentration to one of lower concentration, and so osmotic differences could not come to pass, and consequently no movement of water).

From these observations and theoretical views sprang the interest of the physical chemists in the whole problem of osmosis, and we see constructed the various "osmotic cells" that may be seen in any physico-chemical laboratory. Pfeffer was again pioneer here. He conceived the idea of supporting the "precipitation membranes" that Moritz Traube had described before him in the walls of a porous pot in order to enable them to withstand pressure. Such "precipitation membranes" may be made of many different substances, but the best and commonest is prepared by allowing the solution of a copper salt and the solution of a ferrocyanid to move into the wall of a porous pot from opposite sides. Where they meet a precipitate of copper ferrocyanid is deposited. The copper solution may now be washed out of the pot and the ferrocyanid rinsed off the outside. In the wall of the pot remains a "precipitation membrane" of copper ferrocyanid. This membrane allows water to pass through it easily, but it will not permit substances dissolved in this water to get through. The membrane is therefore "semi-

permeable," and so identical with the "osmotic" membrane postulated by PFEFFER to surround the living cell. If the laboratory cell is filled with a solution of any kind and placed in water, water is sucked into the cell; if it is placed instead into a stronger solution, water is sucked out. When equally concentrated solutions exist within and without, no movement of water occurs. As readily apparent, this behavior corresponds, when viewed superficially, with what PFEFFER and DE VRIES observed in living cells.

PFEFFER made many osmotic measurements with his laboratory cell, and on the basis of his observations VAN'T HOFF some years later formulated his famous laws. These are as follows:

(1) At constant temperature the osmotic pressure of dilute solutions is proportional to the concentration of the dissolved particles.

(2) At the same temperature equal volumes of all dilute solutions having the same osmotic pressure contain the same number of dissolved particles.

(3) At constant volume the osmotic pressure of any solution increases as the absolute temperature.

The work and conclusions of VAN'T HOFF and the physical chemists now became retroactive and the attempt was made to apply the laws of VAN'T HOFF not only to the biological facts that DE VRIES and PFEFFER had furnished in their studies of plant cells, but also to those added by HEDIN, HAMBURGER, GRYNS, KOEPPE, LOEB, HÖBER, OVERTON, WEBSTER, etc., in their work with various animal cells. To this end the observations made on plant and animal cells were compared with those made on the laboratory osmotic cell. When a solution of any electrolyte or non-electrolyte was found not to change the volume of liquid in a laboratory osmotic cell it was said to be "isosmotic" with its contents. Any series of solutions thus isosmotic with the contents of the osmotic cell were therefore isosmotic with each other (and therefore equally concentrated). Similarly, when a solution of any kind was found not to change the volume of a living cell it was said to be "isotonic" with the cell contents. In this way the solutions of many different substances were compared and their "isotonicity" determined. If the laws of osmotic pressure were active in living protoplasm it was to be expected that all "isotonic" solutions should prove to be "isosmotic."

When the first rough comparisons were made it was, in fact, thought that the isotonic solutions were isosmotic, but this conclusion could not stand the pressure of more careful and more numerous observations. *To-day we may safely say that we do not know a single cell for which the laws of osmotic pressure are valid.*

We need not go into details to prove this. If cells obeyed the laws of osmotic pressure they ought always to have the same volume in isosmotic solutions of different substances. Exceptions to this conclusion are the *rule*. This was first proved for the red blood corpuscles by KOEPPE and is corroborated for muscle by the experiments of LOEB, WEBSTER, OVERTON and my own, as described in the earlier pages of this book. Again, with every increase in the concentration of the medium surrounding a cell we should get a *proportionate* decrease in the volume of the cell. As a matter of fact, the shrinkage is always less than anticipated. KOEPPE found that red blood corpuscles always shrink *less* than expected when the concentration of the surrounding medium is raised. The same is true of muscle, living frogs (DURIG), enucleated eyes, nerve tissue and amputated frog legs. While in the osmotic cells of our physico-chemical laboratories electrolytes and non-electrolytes are equally active when the same number of dissolved particles are present in the unit volume, this is not the case in living cells. Generally speaking, the electrolytes are here active out of all proportion to the non-electrolytes.

But aside from these physico-chemical facts which stand so immovably against any belief which sees in living cells a replica of the artificial osmotic cells of our laboratories, biological considerations make the whole conception impossible. To have the laws of osmotic pressure tenable for living cells we must have semipermeable membranes about them. Only as this is the case can changes in osmotic pressure become available for the movement of water into and out of cells. If now, for the sake of argument, we grant this assumption, then no dissolved substances can get into or out of the cell. Such a conception of the cell is impossible, for how under such circumstances could it get its necessary food, or how could it rid itself of its various metabolic products? Both processes are absolutely indispensable for the continuation of life. To get around the difficulty various observers have made these osmotic membranes permeable to some or many dissolved substances. But the moment we grant this,

then the dissolved substances can diffuse from regions of higher to regions of lower concentration, and so differences in osmotic pressure are equalized and no forces remain available for the movement of water. *The adherents to the view that "osmotic" membranes exist about cells can take their choice, they can either utilize their conception to make water move or they can make their membranes permeable and so have dissolved substances move, but they cannot have both. Yet for life to go on in the cell both processes must be able to go on uninterruptedly.*

A further argument against any belief in semipermeable membranes about cells is found in the fact that in no cell studied has such ever been found by the examining eye.

The morphological cell wall is admittedly not concerned in the osmotic activities of the cell. Usually the layer of protoplasm just inside this is considered the so important semipermeable membrane. This layer in plants differs in appearance from the rest of the cell protoplasm no more than the outermost edge of a leukocyte or an erythrocyte differs from the rest of the cell body. But in spite of this negative morphological finding such a semipermeable membrane might still exist. Such a supposition, however, encounters trouble as soon as the fact is recalled that when a cell is cut in pieces or when the contents of a cell are squeezed out into a solution of any kind, these cell fragments (which assume a spherical shape) behave just as the uninjured cell did before. This observation, which it seems to me points decisively against the existence of semipermeable membranes, has been accounted for by saying that the fragments form a new semipermeable membrane about them as soon as they come in contact with the solution into which they are dropped —supposedly in much the same way as new precipitation membranes may be formed in physico-chemical experiments. But in physical chemistry this formation of new precipitation membranes is not so universal an affair; it occurs only when two so-called membrane-forming solutions are brought in contact with each other, and it is hard to conceive of protoplasm being able to form a semipermeable membrane with just any solution with which it is brought in contact. The attempt may be made to meet this objection by saying that it is the universally present fat-like constituents (the lipoids) of the tissues which go to form the membrane when the cell fragments are dropped into any

watery solution, but as we shall soon see, the permeability of the lipoids to dissolved substances is far too limited to help us much toward an understanding of the phenomena that we are discussing.

An enormous literature has sprung up about this question of "membranes" surrounding cells. From the original osmotic membranes of PFEFFER, which were semipermeable, we have come to those which are partially permeable and then to those which are permeable sometimes and then again not. But even these complicated notions encounter trouble, for there is so little connection between the kind of substances that enter cells and those that do not. Only the members of one group—that which has a ready solubility in the fats—have been recognized as having one property in common, and to account for their ready entrance into the cells the osmotic membrane about cells has been endowed with lipoid characteristics. The unfortunate part about this theory, which is in essence that of E. OVERTON, is that while it renders easier our conception of the absorption of these lipoid-soluble substances, it makes it impossible to get the ordinary salts and water into cells, for these are not particularly soluble in these lipoids. OVERTON has, in fact, come to such a conclusion. And yet we know from physiological and pathological facts that all these types of substances must be able to get into cells.

Moreover, what do we gain when we have succeeded in getting any dissolved substance or water through any kind of membrane postulated to exist about a cell? It would collect here and we should still have to account for the movement of the dissolved substance or the water into or through the rest of the cell protoplasm. *There are no membranes about cells. All the phenomena which are difficult to explain when we assume membranes to exist about cells are readily interpreted without recourse to such postulates on the basis of the colloid constitution of protoplasm.*

In answer to these arguments some of my critics have retorted that a "membrane" exists whenever two phases come in contact with each other. At this point we have to stop and define terms, for here the argument begins to become academic. A drop of any fluid, a drop of any colloid solution, a drop of protoplasm or a cell has a "membrane" about it, but this "membrane" is simply a surface tension film; it has nothing in common with

the " osmotic " membranes that in turn the botanists, the physical chemists and the original animal physiologists who worked in this field talked about. These surface tension films are chemically identical with the rest of the cell protoplasm and (except as colloid particles tend to collect in these surface films and so raise their concentration here) as such behave toward water or dissolved substances exactly as does the rest of the cell protoplasm.

These facts indicate clearly that there is little reason for accepting the osmotic theory as of paramount or even great importance in explaining the ways and means by which tissues absorb or secrete water.

I would like to be correctly understood in this matter. I am not maintaining that the laws of osmotic pressure *may* not account for *some* of the phenomena observed in at least *some* cells. This is a question which on the basis of the experimental data now available cannot be decided, but the biological significance originally attributed to these laws has certainly been much overrated. Nor does such a decision against the rôle of osmotic pressure in these biological phenomena minimize in the slightest the value of the work of that score of investigators who have busied themselves with this problem—they have made not only the best effort to analyze physico-chemically the forces active in the absorption and secretion of water by the cell and its myriad associated problems, but they have laid down the experimental data upon which all subsequent workers on this problem must build.[1]

3. Criticism of the Lipoid Membrane Theory

In an attempt to meet the inadequacies of the osmotic theory of water absorption by protoplasm, E. Overton [2] assumes that the surface of cells is made up of a substance which in its properties as a solvent is not unlike ether or the fatty oils. He was led to this conclusion in attempting to account for the fact that many substances when dissolved in water are unable to " plasmolyze " cells. For example, while the various salts, at a suitable concentration, lead to a shrinkage of plant cells, a large number

[1] For new and striking evidence against the osmotic notion of water absorption by cells see Wade W. Oliver: Science, **40**, 645 (1914).

[2] E. Overton: Vierteljahresschr. d. naturf. Gesellsch. zu Zürich, **40**, 1 (1895); **44**, 88 (1899); Zeitschr. f. physik. Chem., **22**, 189 (1897); Pflüger's Arch., **92**, 261 (1902); Nagel's Handbuch der Physiologie, **2**, 2te Hälfte, 744 to 896 (1907).

of other chemical compounds, such as urea, glycerin, various sugars and alcohols do not do so.

Believers in the osmotic theory of DE VRIES and PFEFFER explain this exceptional behavior by saying that the membranes assumed to exist about cells are permeable to this group of substances. OVERTON has tried to define the nature of this permeability by pointing out that all these substances have the property in common of being soluble in fats and fat-like bodies, and as such are universally present in protoplasm (as the lipoids—lecithin, cholesterin, protagon, cerebrin), he has tried to account for the permeability of cells to these substances by saying they go through these cell membranes because they are soluble in them. Most salts, he says, do not go through because they are insoluble in this surface film, in consequence of which they may extract water from the cell and so lead, at the right concentration, to its plasmolysis.

The difficulty with OVERTON'S explanation is that in accounting for the entrance of the lipoid-soluble substances, he makes it impossible to explain the entrance of that much larger group, of which the acids, alkalies and salts are representatives, the vast majority of which are not soluble in fat-like bodies. Even our foodstuffs and the products of cell metabolism belong in good part in this group. Yet, judging from physiological experiments, we know that these *must* be able to enter cells, otherwise how could we account for the normal life or the marked variations in it which we are able to produce by means of these very substances? It is not enough to say that any or all of these substances move only through the intercellular substances. That certain substances in certain tissues *may* move more easily through the intercellular substance than through the cells themselves is not questioned—salts, for example, do not diffuse with the same ease through different colloids—but that does not alter the main contention that salts and many other substances not soluble in the lipoids can and do pass into and through the cells themselves.

Again, the assumption that cells are surrounded by a fat-like membrane makes it impossible to account for the entrance or exit of *water* from the cell. Water is not soluble in the fats (except theoretically), and hence cannot pass through a layer of it, and yet we know that in exceedingly short periods of time cells are

capable of absorbing or secreting enormous amounts of water. The attempt might be made to explain this absorption of water by calling attention to the colloid properties of at least some of the lipoids—lecithin, for example, which is capable of absorbing water when dropped into it (HÖBER). But as soon as we accept this as true then our reasons for the non-entrance of the salts fall away, for when a lipoid absorbs water it loses at the same time its property of being solvent only for lipoid-soluble substances.

What, again, do we attain when such have penetrated the lipoid surface membrane? We accomplish only an accumulation of the absorbed substance within the membrane itself, and just inside of this. We have then to explain how it gets through the rest of the cell.

In the attempt to harmonize these conflicting notions, NATHANSOHN [1] has assumed the surface of cells to represent a sort of mosaic, a part of which is formed by fat-like substances, another by " protoplasmic material " possessed of the properties of a semipermeable membrane. The objections that must be raised against NATHANSOHN's conception are clearly a combination of those that were formerly raised against the osmotic conception alone, plus those that can be lodged against OVERTON's modification of it.

The view of NATHANSOHN is, however, valuable because it brings out the idea of a mixture in protoplasm of substances having fat-like characteristics with such as do not possess this property. But to confine this mixture to the surface of cells is wrong because too limited. *We encounter no difficulty in explaining the various experimental facts at our disposal by ignoring altogether the existence of semipermeable or partially permeable membranes about cells. The substance of a cell consists of a mixture of different colloids. A part of these are colloid proteins with physical and chemical properties like those of fibrin, gelatin, etc.; a second part, colloid lipoids, which, while sharing some of the properties possessed by the proteins, as their power of swelling in water, have specific properties, such as their better power to take up substances soluble only in the fat-like bodies; a third part is made up of the colloid carbohydrates.*[2]

[1] NATHANSOHN: Pringheim's Jahrbücher, **39**, 607 (1904). A review is found in HÖBER: Physikalische Chemie d. Zelle u. d. Gewebe, 2d Ed., Leipzig, 176 (1906).

[2] For a more detailed discussion than is possible in these pages of the problem of fat in the cells see MARTIN H. FISCHER and MARIAN O. HOOKER:

4. Adequacy of the Colloid-chemical Theory of Absorption and Secretion

Let us now see what sort of a substitute for, or addition to, our present conceptions regarding the forces active in absorption and secretion is found in the rôle of the hydrophilic colloids. What can the colloid-chemical theory of water absorption do with the unexplained physiological facts detailed above?

Two substances have always stood out prominently as exceptions to the laws of osmotic pressure as considered active in protoplasm, the acids and the alkalies. The various tissues which have been examined in their dilute solutions all show an absorption of water vastly greater than can be accounted for on the basis of osmotic pressure. In fact, the amount that muscle can swell in dilute acids has been employed by OVERTON as a conclusive argument against the ordinary osmotic conception of water absorption by different tissues. He has pointed out that were all the proteins, carbohydrates and fats contained in muscle split into their simplest products, a sufficient yield of molecules and ions would not be obtained to furnish an osmotic pressure adequate to account for the amount of water absorbed. *We have no trouble in explaining this behavior of acids and alkalies on a colloid basis.* The acids and alkalies are among the substances most powerful in increasing the hydration capacity of protein colloids. In this way we can account for the large amounts of water absorbed in the presence of traces of acid or alkali by red and white blood corpuscles, spermatozoa, muscle, the epithelial cells of the bronchi, intestine, bladder or esophagus, etc.

There is also no difficulty in accounting for the unequal swelling of cells in osmotically equivalent solutions. This is true of the swelling of such simple proteins as fibrin, gelatin and gluten. In fact, the same substances which exhibit an exceptional behavior in the " osmotic " study of cells show a like behavior in the case of simple proteins.

To find an analog for the failure of muscle, red blood cor-

Science, **43**, 468 (1916); Fats and Fatty Degeneration, New York (1917). The rôle of the colloid *carbohydrates* is also ignored in this discussion because little of immediate interest to us has as yet been done with them. They are unquestionably of tremendous physiological and pathological importance, not only in plants but in animals as well.

puscles and cells in general to shrink the calculated amount with every unit increase in "osmotic" concentration is also simple. We need only to refer once more to the swelling of fibrin or of gelatin in which we found that here, too, doubling the concentration did not halve the volume—the amount of decrease was always less than anticipated.

In making the colloids responsible for the amount of water held by the tissues we escape all need for membranes.

We can dispense with them in considering the absorption and secretion of water by cells just as we can in considering the absorption and secretion of water by powdered fibrin or gelatin. Nor are we surprised when fragments of a cell behave toward external conditions as did the whole; in fact, we expect this, for colloids constitute the body of the cell, and just in so far as the colloids in the different parts of the cell do not differ from each other, in so far also do we not expect the processes of absorption and secretion in these various parts to differ. The absence of a visible membrane does not annoy us—it simply indicates homogeneity of the protoplasm. The presence of a visible (not simply "osmotic") membrane (such as a cellulose cell wall) interests us much more. It introduces another colloid, and with it all the possibilities arising therefrom, for all colloids, so far as water absorption is concerned, do not react in the same way either quantitatively or qualitatively toward any given set of external conditions. For this reason the protoplasm of a plant cell shrinks away from the surrounding cellulose wall when immersed in a concentrated salt solution, and is limited in its subsequent expansion if removed to water, for the colloids constituting the cellulose wall are not affected in so marked a way by low concentrations of acid, alkali or salt, as is the protoplasm within it. The possibility of explaining the whole problem of inequalities in the amount of water held by *different parts* of the *same cell* therefore evidences itself here.

What holds for the single cell holds also for *different cells*, in consequence of which we are not surprised when with variation in the colloid constitution of different cells we find a corresponding difference in their behavior when subjected to the same set of external conditions. Under normal circumstances different cells contain unequal amounts of water, and in states of excessive turgor (œdema) neighboring, but morphologically differ-

ent cells may show most unequal degrees of swelling. Whether we deal with different parts of the same cell or with different cells does not matter, we need no semipermeable or other kind of membrane to explain this. The absorptive powers of the various hydrophilic colloids are simply not the same or a colloid common to all the cells has been made to swell more in one place than in another by changes in its surroundings.

Let it be added that we are now able to explain the variations in the water content of the much neglected *intercellular substances*. In discussing water absorption by cells the intercellular substances are all too often overlooked, and this in spite of the fact that under physiological conditions some of the largest amounts of water are stored in tissues containing few cells (as the bell of the jelly-fish or WHARTON'S jelly of the umbilical cord), while in pathological states the very tissues in which cells are fewest, and intercellular substance most conspicuous, may grow richest in water. We need but recall the intense œdemas of connective tissue or the pathological changes characteristic of myxœdema. If we bear in mind that these intercellular substances are, like the cells themselves, but mixtures of different hydrophilic colloids, none of this surprises us.

5. Absorption and Secretion of Dissolved Substances by Protoplasm.

Thus far we have discussed only the absorption and secretion of *water*. We have now to consider the *dissolved substances* in the water. To emphasize what should be self evident, *we cannot and must not consider the absorption or secretion of water and the absorption or secretion of a substance dissolved in the water as identical processes*. Workers in biology make this mistake constantly. The processes of the absorption of water and of the absorption of dissolved substances do not parallel each other in simple physicochemical experiments, and so need not, and do not, in living cells. The two are frequently *associated*, and may at times lie so closely together that they give the impression of running parallel with each other, but they are at all times independent of each other and may even take place in opposite directions at the same time. As we shall see later, a tissue may be absorbing a salt while it is secreting water, or *vice versa*.

For the absorption of water by tissues we have made the

hydrophilic colloids and changes in their state chiefly responsible. The colloid proteins appropriate the lion's share in this matter, but the colloid lipoids and the colloid carbohydrates,[1] in so far as they have capacity for holding water, must not be ignored.

The absorption of *dissolved substances* is quite independent of the amount of water absorbed (except as the absorbed water retains the characteristics of ordinary water and so increases the bulk of solvent available for water-soluble substances in the cell). Since in our criticism of the osmotic theory of water absorption we have incidentally destroyed the mechanism which different authors have used to explain the peculiarities noted in the absorption and secretion of dissolved substances by protoplasm, we need to state how on the colloid basis we are going to account for them.

The troublesome element in the whole problem is summed up in the observation that when any soluble substance is introduced into a living organism it does not distribute itself uniformly throughout that organism. When we drop a crystal of some dye into a cylinder of water we know that after a while the dye by a process of diffusion comes to have the same concentration in all parts of the liquid. The same dye (or any other substance, be this oxygen, a salt, a foodstuff or a medicinal agent) introduced into a living animal spreads through its tissues by a process of diffusion also, yet in the end one organ or one type of cell or different parts of one and the same cell may be stained to different degrees. Supporters of the osmotic theory have tried to account for such phenomena by saying that the osmotic membranes about cells possess a "selective permeability" which lets some substances through while it holds others out. In this way they believe dissolved substances to be kept apart in neat but differently concentrated packages throughout the living organism. But since we found it necessary to give up our belief in such membranes, we have to seek an explanation on another basis. *Concentration differences can be maintained in different parts of the same cell, between different cells or between cells and their surrounding media even in the absence of "membranes" because of inequalities in distribution, determined by solubility, adsorption or chemical differences, or all three together.*

What this means may be illustrated as follows:

[1] See footnote 2, page 203.

(a) Inequalities in Distribution Due to Inequalities in Solubility

When a solution of iodin in water is covered with a layer of ether and the whole is shaken, we can see even with the naked eye that the iodin is ultimately present in different concentrations in the two liquids. While scarcely any remains in the water, the ether assumes a deep color from the iodin. The process is simply a homely illustration of the everyday chemical procedure of "shaking out with an immiscible liquid." The extraction of the iodin from the water depends upon the fact that iodin is soluble in ether, and so decidedly more so in this than in water that practically all moves over into the ether phase. The ultimate state of equilibrium attained, characterized by this very unequal distribution (partition) of the dissolved substance between the water phase and the ether phase, is in this case simply due to the difference in the relative solubilities of the iodin in the two solvents. The proportion of iodin dissolved in each of of the two phases—in this case a concentration of iodin about nine times as high in the one as in the other—is always constant. We call this *the distribution coefficient* or *coefficient of partition.*

In discussing the living cell we have so far spoken of its solvent powers chiefly from the standpoint of its water content. If the cell had solvent powers determined only by its water content, it is obvious that dissolved substances could never appear in it in higher concentrations than those in which these substances are present in the media surrounding the cell. But such a conception of the cell is too limited. In addition to water, most of the various cells of all living organisms contain fat, and the already mentioned fat-like bodies known as lipoids (lecithin, cholesterin, cerebrin, protagon). We can see in advance that living cells containing fats or lipoids must be able to take up (that is, dissolve or absorb) many substances which are better soluble in such fats and lipoids than in water, in greater amounts than the media surrounding these cells which are not so rich in or lack these compounds entirely.

We are indebted to Hans Meyer [1] and E. Overton [2] for recognizing the great physiological importance of the facts here

[1] Hans Meyer: Arch. f. exp. Path. und Pharm., **42**, 109 (1899); ibid., **46**, 338 (1901).

[2] E. Overton: See reference on page 201.

outlined. By methods which we need not discuss here, they found it possible to differentiate between substances which pass into or through cells but slowly and those which do this rapidly.

To the compounds which diffuse rapidly into protoplasm belong the monatomic alcohols, aldehydes and ketones, the hydrocarbons with one, two and three chlorin atoms, the nitro-alkyls, the alkylcyanids, the neutral esters of inorganic and many organic acids, anilin, etc. The diatomic alcohols and the amins of monatomic acids pass into cells more slowly, and still more slowly glycerin, urea and erythrite. The hexatomic alcohols, the sugars with six carbon atoms (hexoses), the amino-acids and the neutral salts of the organic acids diffuse into cells only very slowly.

A glance at this list shows that we have to deal with all manner of chemical substances. Some are relatively simple in composition while others are very complex; some are of physiological importance and found normally in the living cell; others are entirely foreign to the living organism. What physico-chemical character have they in common which allows them to penetrate living cells with more than usual ease, and so to stand out from the great group of the ordinary neutral salts, for example, which do so only slowly? They are all more soluble in fat solvents than in water, and therefore pass into and through cells containing fats and lipoids more rapidly than into and through such as do not. With a given cell the rapidity and the absolute amount of any compound ultimately absorbed must depend upon its relative solubility in water and in the fat or fat-like bodies contained in the cells. In other words, it depends upon what is its *distribution coefficient* between the two phases whether any dissolved substance will enter a cell slowly or rapidly, and whether it will ultimately be found in the cell in a greater, in the same or in a lower concentration than in the medium surrounding it.

The importance of these simple facts is self evident. In order that a substance may produce any physiological effect it must first get into the cell. Other things being equal, a quicker and more powerful effect will be produced by a lipoid-soluble preparation than by one not thus soluble.

The marked effects of the anesthetics (chloroform, ether, alcohol, ethyl chlorid) and of various alkaloids (morphin, cocain, atropin) is associated with their fat and lipoid solubility. The

nervous tissues are high in fat and fat-like bodies, and so take up these substances with special avidity. Because of his greater stock of fat solvent, the fat individual demands more anesthetic before going to sleep than does a lean one. Anesthesia, like all intoxication, is a matter not of absolute amount of anesthetic present, but of concentration. The various grades of anesthesia go hand in hand with definite concentrations of anesthetic in certain cells of the nervous system, and it must evidently take longer to attain this concentration in a fat man than in a lean one.

(*b*) *Inequalities in Distribution Due to Inequalities in Adsorption*

Not only may a living cell come to contain in the unit volume a greater or less amount of any dissolved substance than does the surrounding medium because the cell contains better or worse solvents for it, but the cell may do this because of its *adsorptive* powers. These adsorptive powers are associated with the fact that the cell is largely colloid. The general problem of adsorption may be illustrated as follows:

When a dye is dissolved in distilled water a uniformly colored solution results. If the solution is divided and to one-half is added a little finely-powdered charcoal while nothing is done with the other, we find after shaking both that while the control solution remains entirely unaltered, the color largely disappears from the other. The decolorization has not been chemically induced; the pure carbon does not react chemically with any of the constituents in the tube. The powdered charcoal has a great surface, and the action of this upon the dissolved particles of dye has made them accumulate (condense) upon it. The theory of how this surface action is accomplished need not interest us here.

What has been described is an example of adsorption. The charcoal is the adsorbent, the dye, the adsorbed substance.

Any number of substances could be cited as acting under various conditions as adsorbents; and almost any substance may act as the material capable of being adsorbed. Finely-divided kaolin, precipitates of various kinds and inorganic or organic colloids may take the place of carbon in the above experiment, and acids, alkalies and salts can be adsorbed in the same way as the readily visible dye. All adsorbents do not,

however, behave qualitatively or quantitatively in exactly the same way toward any given material to be adsorbed, and different external conditions modify markedly the adsorption exhibited by any given adsorbent. Examples of adsorption are familiar to everyone. The commercial decolorization of beers, sugars, etc., by animal charcoal; the removal of color from a bath by dipping wool, cotton, etc., into it (dyeing); the staining of histological specimens are all examples of adsorption.

The adsorption of any substance by an adsorbing agent is never complete. Charcoal never takes all the dye out of a bath; some always remains behind. The distribution of the dye between the solvent and the adsorbent is governed by the laws of equilibrium. After the charcoal has taken up as much of the dye as possible, if the supernatant liquid is poured off and pure water is substituted for it, then some of the dye leaves the charcoal and goes back into solution in the water. In this way we can again wash all the dye out of the charcoal. Conversely, when the charcoal has taken up as much dye as it will from a given dye bath, it will proceed to take up an additional amount if more dye is added to the supernatant liquid.

The relationship between the concentration of the substance to be adsorbed and the amount taken up by the charcoal is an interesting one and may be thus stated: From relatively dilute solutions the adsorbent will take up much, from more concentrated solutions relatively less, of the substance to be adsorbed. In other words, if at a certain concentration we can take four-fifths of the dye present in a solution out of this with a given amount of charcoal, then if the dye has a higher concentration we can take out only less than four-fifths, or if it has a lower concentration, more than four-fifths.

Protoplasm behaves toward substances dissolved in a medium that surrounds it in an entirely similar way. Upon this depends the fact that it may contain the same, a higher or a lower concentration of any dissolved substance than the medium surrounding it. Since the protoplasm (adsorbent) of different cells is not the same, it comes to pass that while they are all bathed by the same blood and lymph they nevertheless do not all adsorb the same amount of the proffered materials. In other words, equilibrium is not attained between the protoplasm of different cells and the medium surrounding these at exactly the same

point. Hence it comes to pass that the salt content of the blood, or its content of a dye, a chemical or an immune body, may not only be unlike that of the cells, but that it need not be the same in different cells.

The adsorption properties of protoplasm are markedly influenced by various external conditions [1] exactly as are those of a laboratory adsorbent. Thus, if acid is introduced into protoplasm, its adsorption powers change markedly. In this way a cell or tissue which, under normal circumstances, acts as an excellent adsorbent for a dissolved substance, may practically lose this property or, conversely, one which before adsorbed a given substance only poorly may now take this up with avidity.

(c) *Inequalities in Distribution Due to Specific Chemical Differences*

A third reason why a cell may contain substances in a higher (or lower) concentration than the medium surrounding it resides in the fact that it contains substances capable of combining with the proffered dissolved substance. Thus, if a cell contains iron, it may be expected to take up more of a proffered substance capable of combining with this iron (say a ferrocyanid) than a cell devoid of it or containing it in less amount. We need not multiply such illustrations, for the list is as long as the list of chemical reactions capable of ensuing between the various substances found in any living cell and the substances that come normally or abnormally in contact with it.

The "specific absorption" and consequent "specific effect" of various pharmacological preparations, of "toxins," of "ferments," etc., is generally regarded as an expression of such inequalities in distribution due to specific chemical differences.[2] This point of view is largely correct, but it is well to emphasize that it is likely to be carried too far. We are still too strongly under the influence of the "purely chemical" point of view in this matter. We have already learned that many of the "specific" immune reactions are not so intensely "specific"; and the

[1] See page 644, and such works as L. Pelet-Jolivet: Die Theorie des Färbeprozesses, Dresden (1910).

[2] Paul Ehrlich: Sauerstoff-Bedürfnis des Organismus, Leipzig (1885); Deutsch. med. Wochenschr., 597 (1898); Collected Studies on Immunity, translated by Bolduan, New York (1907). Heinrich Zangger: Vierteljahresschr. d. naturforsch. Gesellsch. in Zürich, **53**, 408 (1908).

whole realm of colloid-chemistry is dotted with examples of reactions that were looked upon as "chemical," when further analysis showed that the "specific" in these reactions did not depend so much upon the presence of certain chemical compounds as upon the physical states in which the components entered into the reactions.

Were we at this point to sum up *our conception of the structure of protoplasm* as thus far developed, we could liken it fairly accurately to *a mass of protein intimately mixed with more or less fat-like material (the fats and lipoids) and carbohydrates (glycogen), the whole being under physiological conditions immersed in a liquid (pond water in the case of an ameba, or lymph and blood in the case of our body cells) from which the protein-fat-carbohydrate mixture soaks up a certain amount of water as well as a certain amount of the various dissolved substances found in the water. The water absorption is governed by the state of the hydrophilic colloids. The absorption of dissolved substances is a matter of equilibrium between the concentration of those found in the medium outside the cell and that of the same substances found in the cell itself.* We have indicated how *solubility characteristics, phenomena of adsorption and chemical combination influence the point at which equilibrium is reached.* This simple picture of the cell furnishes to our minds an adequate conception of its main structure.

PART THREE

ŒDEMA

PART THREE

ŒDEMA

I

INTRODUCTION

The foregoing pages have brought evidence indicating that the colloids of the tissues and their state are chiefly if not entirely responsible for the amount of water they hold under various conditions. *The problem of œdema is also but a problem in colloid-chemistry, the problem of the ways and means by which the normal hydration capacity of the body colloids is heightened.*

We have had occasion to discuss the great contributions first made by the plant physiologists and later adopted by the animal physiologists to this general question of excessive turgor as observed in various cells. We have now to consider the contributions made by the pathologists to this same question, which they, however, discuss under the heading of œdema.

I deem it purposeless to review in detail all their theories. Such a task would not be easy, for the contentions of the various authors cannot always be stated in brief and do them justice. Too often this is because they have mixed their excellent experimental findings with the particular hypothesis which they were attempting to make into a theory; and too often also do we find good attempts to account for œdema on a mechanical basis mixed with the vague conceptions of the activities of "living" protoplasm. Any effort, therefore, to analyze the contributions of an author to the general subject of the nature and the cause of œdema must distinguish carefully between the value of that which he may have contributed to the *experimental* side of the subject and to the *theoretical*.

Richard Bright made one of the first attempts to account for œdema when he tried to find in the loss of albumin from the body in nephritis a cause for the thinning of the blood (hydremia). Such hydremic blood, he reasoned, would then pass easily through the blood vessels and into the tissues, and so cause the latter to

swell. An experimental investigation of BRIGHT'S hypothesis forms the basis of the much-discussed work of JULIUS COHNHEIM and LUDWIG LICHTHEIM.[1] These authors found that the injection of enormous quantities of sodium chlorid solution into the veins of various animals did not bring about an œdema similar in distribution to that observed in BRIGHT'S disease, and so decided that hydremia alone, or a hydremia connected with an increase in the amount of blood circulating in the blood vessels (hydremic plethora), could not be responsible for the œdema of nephritis. Experiments carried out by a number of authors since the work of COHNHEIM and LICHTHEIM confirm, in the main, their findings.

For the older hydremic theory, COHNHEIM and LICHTHEIM substituted what we may call for short the *pressure theory* of œdema so widely accepted by pathologists to-day. Briefly formulated, it holds that variations in the pressure of circulating liquids (such as the blood or lymph) are chiefly responsible for the variations in the amount of water held by the tissues, in that through changes in pressure the circulating liquids are supposed to be forced through the vessel walls into the tissues. It is not strange that this belief should have originated and seemed especially acceptable to those biological workers whose interest centers particularly in animals which possess the conspicuous feature of a circulatory system. But the very school which originally laid most stress upon this force—the school of pathologists and the earlier physiologists—has found its efforts to increase the amount of water held by tissues through an increase by experimental means of the blood and lymph pressures, to result in failure.

To meet the deficiency there was therefore added to the changes in pressure a second element—a change on the part of the involved tissues themselves. Thus COHNHEIM himself recognized that severe œdemas occur in animals when no alteration whatsoever in blood pressure is apparent. To account for them under such circumstances he invoked an "increased permeability of the blood vessel walls." Such a belief has never been proved experimentally, and, indeed, of what consequence would it be from a pathological standpoint? To force liquids through blood vessel walls is not to force them into the tissues. And the fluid

[1] JULIUS COHNHEIM and LUDWIG LICHTHEIM: Virchow's Arch., **69**, 106 (1877); also COHNHEIM: Allgemeine Pathologie, 2d Ed., **1**, 430, Berlin (1882).

of an œdematous tissue is very decidedly in the tissues themselves. COHNHEIM's hypothesis would simply squeeze the œdema fluid as far as the outer wall of the capillaries.

A series of other observers have expressed the tissue factor in yet other terms. We read that in addition to changes in blood pressure there are also necessary for the development of œdema a "loss of elasticity" on the part of the tissue, a "decreased ability to hold back water," a "heightened imbibition," etc. But none of these authors had any clear-cut notion of just how these factors were operative. W. S. LAZARUS-BARLOW's [1] critical and experimental observations are noteworthy in this connection. After emphasizing that anemia of a part as determined by ligation of an artery is commonly followed by œdema and after verifying this observation by experimentally occluding the blood supply to a dog's limb he made the further deduction that an accumulation of "metabolic products" in the affected portion increased such œdema. The latter point he verified by removing the two gastrocnemii from a frog, stimulating the one and keeping the other at rest. On subsequent immersion of the pair in a physiological salt solution the stimulated muscle was found to absorb more water than the non-stimulated. Whether such results were due to a "vital process or one depending upon the osmotic coefficient of the substances produced," LAZARUS-BARLOW could not say.

In 1898 JACQUES LOEB [2] tried to explain œdema in the terms of the osmotic theory of water absorption by defining it as a state of increased water absorption due to an increased osmotic pressure of the cell contents. This was the same explanation which HAMBURGER,[3] VON LIMBECK,[4] GÜRBER [5] and EIJKMAN [6] had previously used to account for the excessive swelling of various cells when subjected to the action of acid or various other changes in their surroundings. Its inadequacy was pointed out by E. OVERTON [7] when he showed that were all the proteins, carbo-

[1] W. S. LAZARUS-BARLOW: Brit. Med. Jour., **1**, 634 and 691 (1895).

[2] JACQUES LOEB: Pflüger's Arch., **69**, 1; **71**, 457; **75**, 303 (1898).

[3] H. J. HAMBURGER: Arc. f. (Anat. u.) Physiol., 513 (1892); 153 (1893); Zeitschr. f. Biol., **35**, 252 and 280 (1897), where references to his earlier papers are found. See also Arch. f. (Anat. u.) Physiol., 31 (1898).

[4] C. VON LIMBECK: Arch. f. exp. Path. u. Pharmakol., **35**, 309 (1894).

[5] GÜRBER: Sitzberich. d. med. phys. Gesellsch. Würzburg, Feb. 25 (1895).

[6] C. EIJKMAN: Virchow's Arch. f. path. Anat., **143**, 448 (1896), where references to his earlier papers will be found.

[7] E. OVERTON: Pflüger's Arch., **92**, 115 (1902).

hydrates and fats contained in our tissues split into their simplest molecules, enough molecules and ions would not result to yield a sufficient osmotic concentration to account for the amounts of water absorbed by such swollen (œdematous) cells. Following this criticism Loeb in republishing his papers struck out all his views on œdema.[1]

But while the theory which Loeb tried to support cannot be upheld (any more than the general osmotic theory of water absorption) he threw out with his rejected œdema views an experimental fact which is of permanent scientific value, and which, if it had been properly appreciated by pathologists and clinicians, would have spared us much of the late literature on this subject. I refer to his experiments carried out with the intention of establishing the fact that *the cause of œdema resides in the tissues.*

II

THE CAUSE OF ŒDEMA RESIDES IN THE TISSUES

A simple experiment proves this. If one leg of an ordinary frog (Rana), a tree frog (Hyla) or a toad (Bufo) is ligated just above the knee as tightly as possible, so that the ligature shuts off not only the venous flow, but also the arterial, and the animal is then placed in sufficient distilled water to cover the legs, *the ligated leg develops an intense œdema*, while the unligated one remains normal. To explain this result recourse cannot be had to the pressure of any circulating liquids, for none such exists, and *so all the conceptions of œdema which regard the pressure, per se, of circulating liquids, as one of the causes, or the chief cause, in the development of this condition, are robbed of their most fundamental support.*

The choice of animals for these experiments was not entirely a random one. It seemed desirable to deal with such in which there exists normally an outside source of water for the tissues, one separate from the ordinary blood or lymph current. Such conditions are satisfied in any of the amphibians. Nevertheless,

[1] Loeb's original paper discussing œdema appears in Pflüger's Arch., **71**, 457 (1898). His collected papers in English appear under the title, Studies in General Physiologie, I and II, Decennial Publications of the University of Chicago, Chicago (1905). What is left of the original article appears on page 501.

an absorption of water may be obtained through the skin of all animals, for my toads developed just as intense œdemas of the leg as did the frogs, and it is a well-known fact that the bodies of dead land animals swell (become œdematous) if kept in water.[1]

The œdemas which these frogs and toads develop are in every way a counterpart of the most intense forms observed clinically. The tissues are boggy, pit on pressure and when incised allow the escape of fluid.

The rate at which the œdema develops in the three types of animals is not the same. It develops and passes away most rapidly in tree toads (Hyla). For toads (Bufo) and ordinary frogs (Rana) the following holds: An œdema of the ligated leg is readily discernible at the end of eighteen hours, and is marked at the end of twenty-four. Within forty-eight hours the swelling approaches its maximum, and may at times be so great that the skin of the ligated leg is ruptured. This maximal swelling is usually maintained some two days, when it begins to diminish.

The diminution in the size of the leg is at first merely due to loss of water, dependent upon changes in the tissues which we shall discuss later. But in the entire absence of a circulation the leg below the ligature cannot, of course, continue to live, and so anywhere from one to two weeks after the ligation, the skin peels and splits and the tissues below it become soft and disintegrate. This loss of substance becomes progressively greater until at the end of three to five weeks only a bony stump covered with tags of tissue may be left.

A number of accessory phenomena are deserving of mention. Twenty-four to forty-eight hours after the ligature has been tied a number of small vesicles usually begin to develop upon the œdematous leg. They are found earliest and most commonly in the tissues of the web of the foot, but they may occur anywhere in the skin below the ligature. The small vesicles, which appear early, gradually increase in size until forty-eight to ninety-six hours after the ligature is tied they become great blebs, which in place of the original water-white or faintly straw-colored fluid

[1] It is needless to point out that the *bloating* of bodies in consequence of the development of *gas* through bacterial action in the gastro-intestinal tract or in the tissues proper is, of course, not referred to in this remark.

found in the vesicles, are likely to contain (especially in toads) a blood-stained serum. After these have persisted a day or two, they rupture and allow the escape of their contents.

The color of the skin of the ligated legs also suffers change. Within twelve hours after the ligature is tied this is usually seen to fade somewhat, and to lose the luster of the healthy skin. At the end of forty-eight hours the color markings, characteristic of the particular species of frog under observation, are much blurred. Late in the experiment (in the second or third week), the ligated leg assumes the gray or grayish-black look of necrosis.

What has been said is illustrated in Figs. 87, 88, 89, 90 and 91. Fig. 87 is a photograph of a frog (Rana), kept in a little water, forty-seven hours after a ligature has been tied as tightly as possible about the left leg. The increase in the size of this leg over the normal right is clearly apparent. Figs. 88 and 89 illustrate the same fact in another frog treated the same way. The tense skin with the blurring of surface markings is easily noted in all three pictures. Later photographs of the frog of Fig. 87 are shown in Figs. 90 and 91. These were taken ninety-five hours after the ligature was tied. Some small blisters which formed between the toes have increased in size to constitute the large bleb seen in the photographs. The œdema in the leg and foot generally is still evident.

While these photographs show us that an œdema develops in a frog's leg even in the total absence of a circulation, they tell us nothing of the severity of these œdemas; in other words, simple inspection of the illustrations does not yield conclusive evidence that the œdemas are as severe as any ever observed clinically. To settle this a few experiments are given in which the œdematous legs were amputated at various periods after their ligation and their weight compared with that of the normal leg of the opposite side.

Experiment 1. *December*, 1907.—One leg is ligated with silk just above the knee in each of four toads (Bufo), and they are placed in separate dishes, each containing enough distilled water (50 cc.) to cover the legs. The ligated legs are found visibly œdematous at the end of twenty hours. The toads are left in the dishes for fifty-four and one hundred and sixty-eight hours, when they are killed, and the two legs are amputated (the ligated one just above the ligature, the other at a corresponding point on the opposite leg), and weighed.

FIGURE 87.

FIGURE 88.

FIGURE 89.

FIGURE 90.

FIGURE 91.

The difference in weight, with the gain on the part of the ligated leg, expressed in percentage of the weight of the unligated leg, is shown in the table.

54 hours, Toad A	Ligated,	0.436 (+26%)
	Unligated,	0.346 (0%)
54 hours, Toad B	Ligated,	0.371 (+25%)
	Unligated,	0.296 (0%)
54 hours, Toad C	Ligated,	0.444 (+45%)
	Unligated,	0.306 (0%)
168 hours, Toad D	Ligated,	2.152 (+82%)
	Unligated,	1.180 (0%)

Experiment 2. *March*, 1908.—Ligatures are tied as tightly as possible just above the knee about the left hind legs of six toads (Bufo). They are placed in finger bowls containing 100 cc. distilled water. After varying periods they are taken out, killed, and the weights of their hind legs compared as already outlined. The results are given in the table:

4.30 hours, Toad A	Ligated,	1.080 (+33%)
	Unligated,	0.810 (0%)
17.30 hours, Toad B	Ligated,	3.350 (+58%)
	Unligated,	2.120 (0%)
28.00 hours, Toad C	Ligated,	4.137 (+80%)
	Unligated,	2.295 (0%)
43.45 hours, Toad D	Ligated,	7.840 (+56%)
	Unligated,	5.020 (0%)
53.00 hours, Toad E	Ligated,	7.262 (+130%)? [1]
	Unligated,	3.152 (0%)
124.45 hours, Toad F	Ligated,	7.160 (+23%)
	Unligated,	5.810 (0%)

[1] The toes of the sound leg are missing. The œdematous leg is practically covered with large blebs.

These experiments prove that the severest grades of œdema may develop in toads and frogs in the entire absence of a circulation. Their validity to do so has, however, been questioned. The objections raised come to this, that in spite of the ligature some sort of a blood or lymph circulation with its ever-adherent "pressure" still exists in the leg. One should, of course, be convinced that no ordinary circulation can continue through the soft tissues of the leg when it is remembered that the ligature is tied as tightly as possible about the leg at a point where musculature is practically lacking. The only other possibility for a circulation would have to be found through the lower end of the femur, and the tissues in and about the knee-joint, whereby

a connection between the thigh above, and the leg below, might be conceived to be continued. These objections are answered by two facts: (1) *If the ligature is tied about one leg of a frog, and the animal is not kept in water, but in a dry vessel, the ligated leg dries up entirely, and this member is carried about in a mummified condition for as long as the experiment is continued.* The rest of the frog dries out more slowly than the ligated leg. (2) *If after ligating the leg the member is amputated and placed in a little distilled water, it shows the same series of changes as though it had been left united to the frog.* We will find abundant evidence of this fact in experiments to be described later. Ocular demonstration of it may be found in Fig. 92. In this are shown anterior and posterior views of two frogs' (Rana) legs forty-nine hours after they had been ligated, amputated, and placed in distilled water. The spreading toes, bulging webs, and swollen leg muscles betray the œdema. Its severity is made apparent when it is stated that both legs have gained over 50 per cent in weight. It would be difficult to conjure up the existence of any orthodox circulation in this experiment with amputated legs.

Experiments 3 and 4 may serve in further illustration of what has been said. In these, tree toads were used. Similar experiments with frogs will be described later and need not be dealt with separately here.

Experiment 3. *December*, 1907.—A ligature is passed about the left leg above the knee in each of two tree toads. The one toad is kept in a dry vessel, the other in one containing a little distilled water. Twenty hours later, œdema is well marked in the ligated leg of the frog kept in water, while that of the frog kept dry is already beginning to shrivel. At the end of fifty-eight and one-half hours the toads are killed, the legs amputated and weighed, with the following results:

Tree Toad A, kept dry	Ligated,	0.071 (−38.8%)
	Unligated,	0.116 (0%)
Tree Toad B, kept moist	Ligated,	0.279 (+78.8%)
	Unligated,	0.156 (0%)

Experiment 4. *June*, 1908.—Three tree toad legs are amputated close to the pelvis. The skin is pulled over the femoral stumps and ligated tightly. The legs are weighed and placed in separate finger bowls each containing 110 cc. distilled water. The first figure in each of the columns is the weight of the tree toad's leg at the beginning of the experiment. After each of the subsequent weighings is given in

A

B

FIGURE 92.

parentheses the percentage of increase in weight over the original weight of the muscle.

Hours in the solution.	110 cc. H_2O.	110 cc. H_2O.	110 cc. H_2O.
0	0.486 (0)%	0.473 (0)%	0.363 (0)%
0.30	0.560 (+15.2)	0.540 (+14.1)	0.417 (+14.8)
1.30	0.600 (+23.4)	0.590 (+24.6)	0.465 (+28.1)
2.30	0.630 (+29.6)	0.620 (+31.0)	0.498 (+37.2)
4.30	0.712 (+46.5)	0.703 (+48.6)	0.557 (+53.4)
6.10	0.795 (+63.5)	0.770 (+62.8)	0.620 (+72.7)
17.35	0.944 (+94.2)x	0.799 (+68.9)x	0.662 (+82.3)x
22.25	0.842 (+73.2)	0.772 (+63.2)	0.627 (+74.7)
28.45	0.780 (+60.5)	0.755 (+59.8)	0.598 (+64.7)
	d	d	

d, d, represent opposite legs of the same toad.
x. At this point the legs are found blistered.

Fig. 93 is based upon the calculations contained in Experiment 4, and represents graphically the course of water absorption

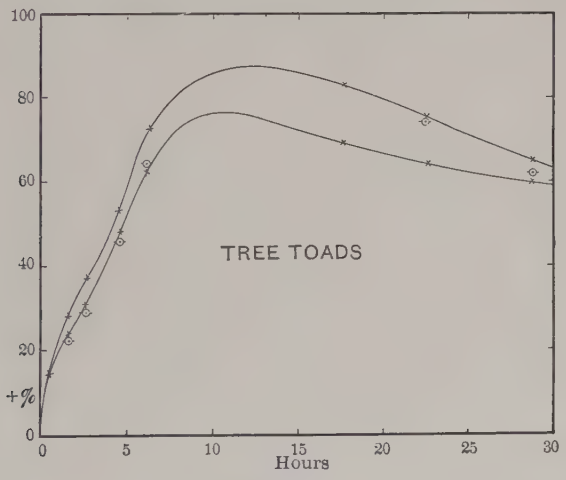


FIGURE 93.

as observed in these three amputated tree toads' legs. The curves show that the initial increase in weight is followed later by a decrease. This corresponds with the ocular observations already detailed on the development of œdema in ligated legs left *in situ*.

After what has been said it will not seem strange that these œdematous changes in a ligated leg occur in a toad or frog just as readily and rapidly when the animal has its central nervous system destroyed as when this is not done. If, however, the animal dies, the difference between the weights of the two legs does not develop. But this is not because the œdema does not develop in the ligated leg—it does just the same—but *an equally intense absorption of water occurs in the other leg which through the death of the animal has been deprived of its circulation.*

These experiments already enable us to cast aside all those explanations of œdema which attribute its development to pressure changes *per se* of circulating liquids. *The cause of œdema resides in the tissues themselves, and these become œdematous not because water is forced into them, but because changes take place in them whereby they are enabled to absorb water from any available source. In the case of the experiments on toads and frogs this available source of water is the water contained in the dishes in which the animals are kept. In clinical cases of œdema, it is found in the fluids which pass through or about a tissue.*

III

ON THE NATURE AND CAUSE OF ŒDEMA

We are now in a position to attempt an analysis of the nature and the cause of œdema. In order to render clear the argument that follows and the purpose of each experiment, we will at once state our conclusion. *A state of œdema is induced whenever, in the presence of an adequate supply of water, the capacity of the colloids of the tissues for holding water is increased above that which we are pleased to call normal. Any agency capable under the conditions existing in the body, of thus increasing the hydration capacity of the tissue colloids constitutes a cause of œdema. The accumulation of acids within the tissues brought about either through their abnormal production, or through the inadequate removal of such as some consider normally produced in the tissues, is chiefly responsible for this increase in the hydration capacity of the colloids, though the possibility of explaining at least some of it through the production or accumulation of substances (of the type of urea, pyridin, certain amins, etc.) which can hydrate*

colloids as can acids, or through the conversion of colloids having but little capacity for water into such as have a greater capacity must also be borne in mind.

It was the purpose of Part Two in this volume to prove that in the colloids of the tissues and in their variable capacity for holding water we have an adequate explanation for the largest amounts of water ever held by tissues under physiological conditions or in states of excessive swelling (excessive turgor, plasmoptysis, œdema). We need now to discuss how the degree of hydration characteristic of normal cells may be so increased that they are judged œdematous. Of the several agencies active here we shall discuss in greatest detail, because we consider it most important, the question of an abnormal production and accumulation of acid in the involved tissues.

Our proof for the truth of the general conclusion stated above will take three directions:

1. An abnormal production or accumulation of acids, or conditions predisposing thereto, exist in all states in which we encounter the development of an œdema.

2. Conversely, any means by which is rendered possible the abnormal production or accumulation of acids in the tissues is accompanied by an œdema.

3. The development of an œdema is antagonized by the same substances which decrease the capacity of hydrophilic colloids for holding water and is unaffected by substances which do not do this.

We will consider these separately:

1. An Abnormal Production or Accumulation of Acids or Conditions Predisposing Thereto Exist in all States in which We Encounter Œdema

§ 1

We are especially prone to see states of œdema develop in conjunction with *circulatory disturbances.* Thus, when the function of the heart is sufficiently impaired an œdema which is more or less general affects the body. It is ordinarily said that because of the disturbance in the circulation an increased capillary pressure results, in consequence of which fluid is

squeezed into the tissues. And yet everyday clinical experience shows that such reasoning is entirely wrong, for if we give our patient digitalis or some other heart "stimulant" which *increases* the blood pressure the œdema gets better, not worse. What we have said regarding a disturbance in the general circulation holds also for the local interferences with the circulation as through thrombosis, embolism, or ligation of an artery or vein supplying any part of the body. If a good collateral circulation exists, the thrombosis, embolism, or ligation may be entirely without effect, or if such a collateral circulation is gradually established the œdema may gradually pass away; but if neither of these is possible, then the œdema persists.

A patient tends to develop a general or a localized œdema whenever an insufficient amount of arterialized blood is being propelled through his tissues, and any general or local condition which produces such a state or aggravates an existing one, aggravates the œdema, and vice versa. This is why postural changes, rest in bed, drugs which increase the effectiveness of the heart's work, and measures which tend to restrict those physiological functions which we know normally to be followed by an increased demand for blood all help to improve an œdema, while the reverse does the opposite.

But how does insufficient flow of normal blood through a tissue lead to an œdema? Is such accompanied by an abnormal production or accumulation of acid? As already stated, this is what we need and know from our previous experiments to be potent in increasing the capacity of the tissue colloids for water. That this is the case is a well-known and long-established fact. When the blood is not carried away from a tissue at its normal rate there tends to accumulate in it and in the tissues drained by it the carbonic acid which is constantly being produced in our cells. It is this carbonic acid which under normal circumstances accounts for the swelling of the red and white blood corpuscles whenever the arterial blood changes to venous,[1] and this tendency is greatly heightened when the normal blood is replaced by the highly venous blood encountered in circulatory disturbances. What happens in the cells of the blood happens also in the tissues and cells drained by that blood. They all tend

[1] See the experiments of HAMBURGER, VON LIMBECK, GRYNS, EIJKMAN, etc.

to swell just as do fibrin flakes in water when the carbonic acid tension in it is increased. The observation of STRASSBURG and EWALD that *the carbonic acid content of œdema fluids and of tissues deprived of a circulation runs very high is therefore one of the factors to be considered in trying to find a cause for the increased capacity of the tissues for holding water in states of disturbed circulation.*

There exists, however, a second and more powerful factor which leads to an abnormal acid production when the circulation is disturbed. This is brought about through the inadequate supply of oxygen to the affected parts. As first proved through the striking experiments of TRASABURO ARAKI,[1] *dogs, rabbits, and frogs excrete lactic acid in their urine in addition to various other abnormal substances* whenever subjected to oxygen want by any means whatsoever. Under ordinary circumstances lactic acid is not found in the urine, but let the oxygen supply to these animals be sufficiently reduced (through confinement in a closed box, through carbon monoxid poisoning, or through the injection of curare, amyl nitrite, or cocain, and the acid appears. Such acid is also found in human beings when through accident or disease they are compelled to suffer from oxygen want. Lactic acid is not the only acid that may be or is produced under such circumstances. E. MENDEL[2] found the phosphoric acid content of the urine increased after epileptic seizures and in apoplexy, and F. HOPPE-SEYLER[3] found various œdema fluids to contain valerianic, succinic, and butyric acids, besides lactic.

The lactic acid found in the urine in conditions associated with a lack of oxygen *is produced in the tissues*, enters the blood, and is excreted by the kidneys. This has been proved by ARAKI'S later work and through HERMANN ZILLESSEN'S[4] experiments. ZILLESSEN found that when the oxygen supply to a muscle or to the liver is shut off for a variable number of hours through ligation of the arteries supplying these parts, an increased production of lactic acid occurs. If the ligature is loosened and the first blood returning from the oxygen-starved tissues is

[1] TRASABURO ARAKI: Zeitschr. f. physiol. Chemie, **15**, 335 and 546 (1891); ibid., **19**, 422 (1894).

[2] E. MENDEL: Arch. f. Psychiatrie u. Nervenkrankheiten, **3**, 636.

[3] F. HOPPE-SEYLER: Zeitschr. f. physiol. Chemie, **19**, 476 (1894).

[4] HERMANN ZILLESSEN: Zeitschr. f. physiol. Chemie, **15**, 387 (1891).

analyzed, this is found to be particularly rich in lactic acid, and if the blood is titrated, it is found to have a diminished capacity for neutralizing a standard oxalic acid solution.[1]

In consequence of circulatory disturbances, whether general or local, an abnormal production and accumulation of carbonic, lactic and other acids occurs which increases the hydration capacity of the colloids of the involved tissues, because of which they then suck water out of the blood and lymph streams bathing them.

§ 2

In place of interfering mechanically with the circulation we may make the tissues suffer from a lack of oxygen, and thus from an abnormal production and accumulation of acid, by interference with the normal oxygen-carrying power of the blood. We find in this a ready explanation of the œdemas so frequently noted in the severe *anemias*, no matter what their cause. It is of interest, therefore, that FELIX HOPPE-SEYLER[2] was able to isolate lactic acid from the urine in two cases of severe anemia. As additional evidence in this direction may be cited R. VON JAKSCH'S[3] findings, amply verified by subsequent workers, that the blood shows a distinctly diminished power of neutralizing acid in *pernicious anemia, leukemia, and chlorosis.* That this decrease in the ability to neutralize acids really means that an abnormal production of acids has occurred in the tissues of the anemic individual, is evident not only from the work of ARAKI and ZILLESSEN already cited, but from VON JAKSCH'S own finding that in carbon monoxid poisoning in which the abnormal presence of lactic acid in the urine has been indisputably shown by ARAKI, there also exists a distinct decrease in the normal capacity of the blood to neutralize acids.

§ 3

An œdema, often of a severe grade, is the almost constant accompaniment of various states of *inanition.* It is observed

[1] ARAKI, ZILLESSEN and most of the earlier observers speak of a "decreased alkalinity" of the blood. Because modern physico-chemical conceptions have changed our old notions of what constitutes alkalinity, it is best to state the experimental findings of these authors as above.

[2] FELIX HOPPE-SEYLER: Zeitschr. f. physiol. Chemie, **19**, 473 (1894).

[3] R. VON JAKSCH: Klinische Diagnostik, 5th Ed., Berlin (1901).

not only in starvation, but in the various forms of scurvy that are observed clinically, and the experimental types that may be induced in animals. What evidence have we for the abnormal production or accumulation of acids in all these conditions? We are, first, not without clinical evidence. The observations on human beings undergoing a voluntary fast all agree in showing that the urine grows progressively more acid with each day of starvation. The only exception to this rule was noted by LUIGI LUCIANI [1] in his study of SUCCI during a thirty days' fast. For the first six days of SUCCI's fasting there was a gradual increase in the acidity of the urine; for the rest of the period it remained very high in spite of the fact that he consumed large amounts of alkaline mineral water.[2] A. E. WRIGHT [3] has made a further observation of interest. He noted a diminution in the capacity of the blood to neutralize acid in seven cases of scurvy.

Yet more convincing are the experimental studies on starving animals. The normally acid urine of the carnivora becomes more intensely so with progressive starvation, and in herbivora, the normally alkaline urine becomes highly acid. The same occurs if animals (especially herbivora) are fed an exclusive diet of any sort. An exclusive oat diet, which is high in acid salts and low in calcium, is quickly fatal. H. WEISKE [4] found that when certain mineral salts, especially calcium salts (which are peculiarly powerful in neutralizing the effects of acid), are added to the pure oat diet the animal fares better. A thorough study of starvation and such one-sided diets, rich in acids and poor in calcium, has been made by AXTEL HOLST and THEODOR FRÖLICH [5]. They describe as constant findings in their experiments the occurrence of œdema. "A pronounced universal anasarca" was noted in all the starved animals, while those fed exclusively on oats, barley, wheat, or some of their derivatives showed various degrees of œdema up to such universal anasarcas.

[1] LUIGI LUCIANI: Das Hungern, 164, Hamburg und Leipzig (1890).

[2] SUCCI's fasting period was long enough to have allowed of the development of an œdema, and yet none is noted in LUCIANI's account of the case. I attribute this to the beneficent effects of the mineral water he consumed. See the effects of alkali and salts on œdematous states as given below.

[3] A. E. WRIGHT: Lancet, **2** (1900).

[4] H. WEISKE: Zeitschr. f. Biologie, **31**, 421 (1895).

[5] A. HOLST and T. FRÖLICH: Journal of Hygiene, **7**, 634 (1907).

Close scrutiny of HOLST and FRÖLICH'S experiments would seem to indicate that the more liberal the variety of the salts in the diets, the less the tendency to observe an œdema.

§ 4

Œdema is a not uncommon accompaniment of *fever*. In some fevers it constitutes a symptom so marked that it is looked for clinically; in others, the increased amount of water held by the patient is clearly indicated by his increase in weight and his failure to secrete an amount of water through kidneys, lungs, skin and bowel, the equivalent of that ingested. With remission or discontinuance of the fever there has been noted by the most careful observers an increase in the output of water by all the water-secreting organs above the amount ingested.

It is not to be assumed, of course, that the fever, *per se*, is the cause of the œdema. It may contribute toward this end, however, for certain proteins absorb more water at a higher temperature than at a lower one. A highly acid urine is characteristic of fevers of the most varied kinds, and VON JAKSCH found a constant diminution in the neutralizing power of the blood for acids. As to the cause for this acid production we are still in the dark; it can be the indirect result of toxic changes induced in organs of the circulation (for example, the heart), but in major part it is consequent upon the action of the poisonous (fever-producing) substances on the tissues generally. We need only call to mind the great inhibition of various oxidations occurring normally in the body and necessary for the continuation of life that various bacterial and animal toxins produce. Any classification of the œdemas is necessarily an arbitrary one, and what I have called here the œdema of fever must ultimately, no doubt, fall into the group of the general toxic œdemas.

§ 5

Œdema is an almost constant accompaniment of certain types of *nephritis*. We cannot, of course, accept the belief that the œdema associated with diseases of the kidneys is dependent upon the increased blood pressure which is found in *some* cases of nephritis. As a matter of fact, the most intense œdemas are encountered in the so-called parenchymatous types of neph-

ritis, the very ones in which we are least likely to note a rise in blood pressure. Nor is it true, as ordinarily taught, that the œdema is consequent upon the kidney disease. It is as primary as the kidney disease itself, as we shall see later.[1]

As evidence of an abnormal production or storage of acids in nephritis we note that the urine of nephritics is generally acid in reaction, and often highly so. More convincing still is VON JAKSCH'S finding that the "alkalinity" (acid-combining power) of the blood is constantly and markedly decreased in the severer nephritides. This existence of a constantly and highly acid urine, and a lowered capacity of the blood to combine with acids, may at first sight seem unconvincing evidence in favor of the abnormal production of acids in this condition and in certain others associated with œdema that we have discussed, but to value it correctly we need only remember that in the severest experimental intoxications with acids, those in which large amounts of acids of known strength are introduced into the stomach, peritoneal cavity, blood, or subcutaneously, no more evidence of the acid intoxication can be found than just such an increased acidity of the urine and decreased acid-capacity of the blood. Furthermore, a change in degree of acidity to which our ordinary indicators respond only indistinctly, shows itself by marked differences in the swelling of colloids.

We learn from ARAKI and ZILLESSEN'S observations that an abnormal production of lactic and other acids occurs in animals whenever they are subjected to want of oxygen by any means whatsoever. In their experiments they used methods which varied from such as act through direct interference with the oxygen supply to the animal (compression of trachea) to such as owe their effect to an action upon the oxidizing ferments of the tissues themselves (hydrocyanic acid). It is of interest, therefore, to note that A. JOLLES, OPPENHEIM,[2] M. C. WINTERNITZ and J. C. MELOY,[3] have found substances present in the blood of nephritics which interfere with at least some of the oxidation phenomena which we know to be necessary for the proper continuance of life.

[1] See page 491.

[2] JOLLES and OPPENHEIM: Münchener med. Wochenschr., **47**, 2083 (1904).

[3] M. C. WINTERNITZ and J. C. MELOY: Jour. Exp. Med., **10**, 759 (1908); WINTERNITZ: ibid., **11**, 200 (1909).

§ 6

We can advantageously consider next what may be called the *œdema of the dead.* After death, as is well known, the acid content of the tissues rises rapidly. In fact it soon reaches such a point that our commonest and coarsest indicators suffice to show its presence. For the most part the acid formed is lactic acid. It matters little what we assume to be either the origin of this acid or the exact chemical change whereby it is produced. The presence of so much acid in the tissues gives us all the conditions necessary for the development of the most intense grades of œdema if only water is available. Since our conception of œdema possesses no " vitalistic " attributes, we are not surprised to find that a *dead body develops an œdema quite as readily, if not more readily, than a living one.* This explains the " œdema " which develops in the dead when they lie in water, and why the intravenous injection of a physiological salt solution which does not lead to an œdema in a living animal is promptly followed by such if done upon the dead. A living frog kept up to its neck in distilled water for several days shows a variation of less than 3 per cent in weight; the same frog after being killed gains progressively until, at the end of sixty hours, it has absorbed from 30 to 60 per cent of its original weight.

§ 7

It is self-evident that what has been said regarding the general œdemas holds also for the *local œdemas.* There is no imaginable difference between the cause for a general œdema, the result of a leaking heart valve, and the cause for the local œdema observed in an *infarcted area,* except that if the infarction is due to plugging of an end artery with an embolus, no increased blood pressure is available for its explanation. But this is not needed, for through the defective blood flow through the part an abnormal production and accumulation of acid occurs in the infarcted area which increases the capacity of the tissue colloids for water, and so they suck it up from their surroundings as does a dead body from the water in which it lies. For this reason the infarct in its earlier history always shows itself as the familiar swollen, firm pyramidal mass, which stands out prominently from the

surrounding tissues. The subsequent decrease in size is due to a combination of changes (coagulation, autodigestion, solution) identical with those observed in tissues laid in weak acid solutions.

The *gangrenes* present the same problem as the local circulatory disturbances. Their chief interest to us lies in the question of whether they will be moist or dry. If water is furnished the dead or dying tissues, either from without or through the blood or lymph circulation, they swell and a moist gangrene results; if this does not happen, we have a dry gangrene. In a gangrene due to closure of a vein, a moist gangrene is therefore to be expected, while a gangrene due to obstruction of an artery is more likely to be dry.

The *local œdemas following the bites or stings of insects* have a special interest. In quite a number of these the sting carries formic or other acids into the tissues. Here we have a direct etiological factor for the production of the local œdema. In others, poisons are injected which have a well-marked reducing power. By this means a local group of cells are placed in a state of lack of oxygen through chemical means. It is worthy of note that originally and during the period of greatest swelling such insect stings are white, and not until later do they become red. The increased blood flow so necessary in most explanations of these local œdemas does not occur until the œdema has begun to subside. *Instead of the blood circulation determining the œdema the œdema determines whether the circulation shall continue through the affected part or not.*

This explanation of the nature and cause of the local œdemas can be further tested. The œdematous *wheals* following bites or stings can be mimicked perfectly with a gelatin plate and a little acid. If with a fine hypodermic needle a little formic acid is stabbed into a gelatin plate, and the whole is then laid into water, *an urticarial-like wheal develops about each spot pricked with the needle*, which in shape and in rate of development is not unlike those which follow the bite of an insect or the introduction of a formic acid laden needle into the skin. This is illustrated in Figs. 94 and 95. In Fig. 94 the surface of a 6 per cent gelatin has been touched in different spots with a needle dipped in formic acid, while in Fig. 95 the prickings have been carried out in a design. The swelling of the gelatin about each of the points touched with the needle is readily apparent.

In Fig. 96 are shown some wheals which developed *accidentally* on the surface of some of my gelatin discs. The particular disc pictured had lain for thirteen days in n/20 hydrochloric acid. The hyaline gelatin does not photograph easily, and so the figure does not indicate how clearly these wheals imitate such as are observed clinically. Those shown here are due to local infections of the gelatin with a mold. In place of the perfectly smooth surfaces which these gelatin discs show ordinarily, we see them here studded with small mounds indicative of irregularities in the absorption of water. The cause for these local swellings may be a twofold one. As the mold developed while these discs were lying in dilute acid solutions, I question whether an additional local production of acid (of which the molds are capable) gave rise to the local swellings. The affected spots are softer than the surrounding gelatin, and later became almost liquid. I think, in consequence, that the gelatin suffers a partial digestion under the influence of proteolytic ferments manufactured by the mold in the affected spots. Such a partially digested gelatin corresponds with the Beta-gelatin of TRAUBE, which we know from WOLF-

FIGURE 94.

FIGURE 95.

GANG OSTWALD'S[1] experiments to be capable of a distinctly greater swelling than ordinary gelatin.

In passing let it be noted that this simple observation teaches how a chemical change in the colloid itself, in this case induced through a ferment—just such a change as might occur in living matter—may affect its capacity for holding water. This is a

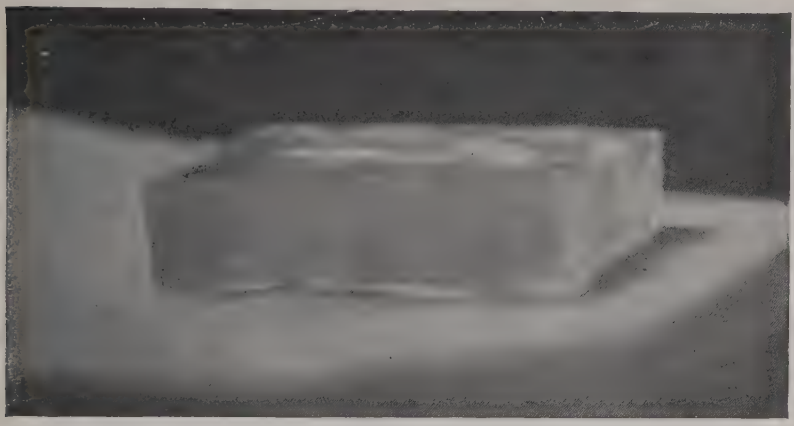


FIGURE 96.

fact not without biological significance in this problem of the ways and means by which a tissue regulates its water content, as we shall discuss in greater detail later.

2. Any Means by which an Abnormal Production or Accumulation of Acid in a Tissue May be Brought about is a Means of Producing an Œdema

We now pass to the second link in our chain of evidence. *Any condition which makes for the production of acid in the tissues leads to the development of an œdema if a source of water is available.*

§ 1

The quickest way to put the tissues of an animal into a condition that permits of the development of acids in them is to

[1] WOLFGANG OSTWALD: Pflüger's Arch., **109**, 277 (1905).

kill the animal. The fact does not surprise us, therefore, that an œdema develops with greater ease in a dead animal than in a living one. If a living frog is kept up to its neck in distilled water it suffers little variation in weight. A change in weight of 3 per cent covers the extremes. But let the frog be killed and be kept similarly covered with water and a progressive rise in weight at once sets in. This is readily apparent from the following experiments:

EXPERIMENT 5. January 3, 1909.—Three frogs which had suffered no appreciable change in weight after residence for several days in distilled water, had the urine expressed from their bladders, were killed, weighed and hung into jars containing distilled water. The original weights of the freshly killed frogs were as follows:

49.5 34.3 39.2

After the designated number of hours in distilled water the weights changed to the following. In parentheses after each weighing is given the percentage of increase in weight (water absorption) as calculated in terms of the original weights of the frogs:

Hours.	%	%	%
10.15	54.8 (+10.7)	39.8 (+16.0)	43.2 (+10.2)
22.00	57.9 (+17.7)	42.2 (+23.0)	45.0 (+14.7)
33.15	59.1 (+19.4)	42.9 (+25.0)	46.8 (+19.3)
52.15	63.0 (+27.2)	46.0 (+34.1)	49.8 (+27.2)
74.00	69.5 (+40.4)	49.2 (+43.4)	55.5 (+41.5)

It is not necessary that the entire body of the frog be covered with water in order to allow such an œdema of the dead to develop. The dead body need only be in contact somewhere with a source of water. In the following experiment only a fraction of the bodies of the dead animals was immersed in water.

EXPERIMENT 6. At 5 P.M., July 19, 1909, five frogs are killed and placed in separate jars, each containing a few cubic centimeters of water. The original weights of the frogs are as follows:

40.0 38.5 35.0 30.5 28.0

Nineteen hours later the frogs have gained in weight thus:

55.5(+38.7%) 48.6(+26.2%) 46.0(+31.4%)39.5(+29.4%)36.5(+30.3%)

§ 2

But we possess subtler methods of producing abnormal amounts of acids in the tissues than by killing our animals. We can use any one of a long series of *poisons.* I chose those which ARAKI used in his experiments on the effects of lack of oxygen. The introduction of these poisons into the bodies of warm or cold-blooded animals he found to be always followed by the production of excessive amounts of various acids (particularly lactic acid) in the tissues. In a series of experiments made with GERTRUDE MOORE, we found that the *injection into the dorsal lymph sac of a frog of any of the poisons used by* ARAKI *is followed by an œdema. Frogs poisoned with morphin, strychnin, cocain, arsenic, or uranyl nitrate all absorb amounts of water which run from* 15 *to* 60 *per cent of the normal weight of the frog.* A frog that has gained even 15 per cent in weight is decidedly œdematous. The œdema in all these cases begins to develop within a few hours after the poison is injected, and becomes progressively worse for twenty-four to seventy-two hours. The severer the intoxication the greater the œdema. If the amounts of poison injected have not been too large, and the animal is given a chance to eliminate it by renewing frequently the water in which the frog is kept, its œdema may be made to disappear entirely, and the animal come out none the worse for its experience at the end of three to six days.

The following experiments may serve to illustrate what has been said:

EXPERIMENT 7. *Morphin Œdema.*—A series of frogs which have been kept in distilled water for several days, have the urine expressed from their bladders, are weighed, injected with various amounts of morphin into the dorsal lymph sac and kept in separate jars containing enough water to cover the legs (100 cc.). The changes in weight are indicated in the table. The first figure in each of the columns shows the original weight of the frog. Above it is indicated the amount and form of morphin injected.

Hours.	0.02 gram morph. hydroch.	0.02 gram morph. hydroch.	0.02 gram morph. hydroch.	0.02 gram morph. hydroch.
	%	%	%	%
0	36.9 (0)	37.8 (0)	35.7 (0)	41.3 (0)
7.00	.....	.....	.....	46.0 (+11.3)
10.15	40.2 (+8.9)	43.1 (+14.0)	43.2 (+21.0)	
22.00	39.0 (+5.6)	43.1 (+14.0)	41.0 (+14.9)	
26.00	.....	.....	.....	44.5 (+ 7.7)
33.15	39.0 (+5.6)	41.1 (+ 8.1)	41.0 (+14.9)	
47.30	.....	.....	.....	43.5 (+ 5.2)
52.15	38.8 (+5.0)	39.8 (+ 5.3)	41.0 (+14.9)	
74.00	37.0 (+0.3)	37.5 (− 0.8)	38.5 (+ 7.8)	
127.00	36.8 (−0.3)	.....	38.0 (+ 6.4)	

A second series similarly treated gives the following result:

Hours.	0.04 gram morph. hydroch.	0.08 gram morph. hydroch.	0.05 gram morph. sulph.	0.037 gram morph. sulph.
	%	%	%	%
0	42.7 (0)	62.0 (0)	48.7 (0)	40.2 (0)
3.30	.....	.....	50.7 (+ 4.1)	45.5 (+13.1)
7.00	48.4 (+13.3)	71.9 (+15.9)		
18.00	.....	.....	58.0 (+19.0)	53.5 (+33.0)
22.00	.....	.....	59.0 (+21.0)	Dead
26.00	49.0 (+14.8)	76.2 (+22.9)	Dying	
47.30	45.0 (+ 5.4)	70.5 (+13.7)		
90.30	45.0 (+ 5.4)	70.2 (+13.2) Still in strychnin-like spasms.		

EXPERIMENT 8. *Arsenic Œdema.*—Three frogs which have been kept in distilled water for four days have the urine expressed from their bladders, are weighed, and injected with the indicated amounts of FOWLER'S solution. The following table of weights is self-explanatory:

Hours.	0.25 cc. Fowler's solution.	0.187 cc. Fowler's solution.	0.125 cc. Fowler's solution.
	%	%	%
0	45.0 (0)	40.0 (0)	38.9 (0)
6.15	50.0 (+11.1)	47.3 (+18.2)	39.0 (+ 0.2)
18.15	Dead	54.0 (+35.0)	43.0 (+10.5)
24.15	.....	57.0 (+42.5) just died	43.0 (+10.5)

EXPERIMENT 9. *Uranium Œdema.*—Six frogs are injected with the indicated amounts of uranyl nitrate and placed in separate glass

jars each containing 100 cc. distilled water. The variations in weight are easily understood from the following table:

Hours.	0.24 gram.	0.24 gram.	0.2 gram.
	%	%	%
0	52.3 (0)	52.1 (0)	51.5 (0)
17.00	58.0 (+10.9)	59.5 (+14.2)	61.8 (+20.0)
22.30	61.0 (+16.6)	62.2 (+19.3)	65.8 (+27.7)
29.30	64.0 (+22.3)	66.5 (+27.6)	70.5 (+36.9)
45.30	66.7 (+27.5)	71.5 (+37.2)	75.2 (+46.0)
53.45	68.0 (+30.0)	75.5 (+44.9)	79.5 (+54.3)
71.00	Killed	77.5 (+48.7)	83.0 (+61.1)
78.00	.....	Dead	Dead

Hours.	0.2 gram.	0.16 gram.	0.16 gram.
	%	%	%
0	51.3 (0)	41.0 (0)	37.8 (0)
17.00	61.2 (+19.3)	52.2 (+26.8)	47.5 (+25.7)
22.30	63.3 (+23.4)	55.8 (+36.1)	48.3 (+27.7
29.30	64.5 (+25.7)	61.5 (+50.0)	52.0 (+37.6)
45.30	65.0 (+26.7)	65.5 (+59.7)	53.8 (+42.3)
53.45	69.0 (+34.5)	Dead	57.0 (+50.7)
71.00	69.0 (+34.5)	.....	58.0 (+53.4)
78.00	71.0 (+38.4) Killed	.....	Dead

In another series of five frogs several injections of uranyl nitrate are made into the dorsal lymph sacs, as indicated below, and with the following results:

Hours.	0.04 gram.	0.04 gram.	0.03 gram.
	%	%	%
0	51.3 (0)	53.2 (0)	46.2 (0)
20.00	55.5 (+ 8.2)	55.3 (+ 3.9)	48.0 (+ 3.9)
	Uranyl nitrate 0.08 gram.	0.08 gram.	0.06 gram.
25.00	56.5 (+10.1)	54.0 (+ 1.5)	47.5 (+ 2.8)
32.30	59.5 (+15.9)	55.0 (+ 3.4)	49.0 (+ 6.0)
	Uranyl nitrate 0.3 gram.	0.24 gram.	0.2 gram.
47.30	61.0 (+18.9)	54.0 (+ 1.5)	50.0 (+ 8.2)
53.00	66.0 (+28.6)	58.5 (+ 9.9)	54.5 (+17.9)
67.00	71.0 (+38.4)	67.0 (+25.9)	63.0 (+36.3)
71.30	Killed	Killed	64.5 (+39.6)
77.00	.....	.....	Dead

Hours.	0.03 gram.	0.02 gram.
	%	%
0	45.5 (0)	38.0 (0)
20.00	48.5 (+ 6.6)	41.0 (+ 7.9)
	Uranyl nitrate 0.06 gram.	0.04 gram.
25.00	48.5 (+ 6.6)	39.0 (+ 2.6)
32.30	50.0 (+ 9.9)	40.5 (+ 6.5)
	Uranyl nitrate 0.16 gram.	0.08 gram.
47.30	50.8 (+11.6)	39.5 (+ 3.9)
53.00	53.7 (+18.0)	41.5 (+ 9.2)
67.00	60.0 (+31.8)	45.0 (+18.4)
71.30	61.5 (+35.0)	43.0 (+13.1)
77.00	63.2 (+38.9)	42.2 (+11.0)
88.30	65.8 (+44.6)	41.5 (+ 9.2)
97.00	68.5 (+50.5)	42.0 (+10.5)
115.00	77.5 (+70.3)	45.5 (+19.7)
120.00	Dead	45.5 (+19.7)
126.30	.....	45.0 (+18.4)
138.30	.....	48.0 (+26.3)
143.00	.....	49.5 (+30.2)
		2 days later, dead.

Of these chemical œdemas, as we may call them for short, we shall have more to say later. Here we would only point out that we find in the list of poisons enumerated above, heart poisons, kidney poisons, nerve poisons, poisons that increase or decrease blood pressure, that increase or decrease lymph flow, that injure blood vessel walls, or have not been proved to do so, etc. Does not this simple fact first of all, seriously question every theory of œdema that would establish any *one* or all of these conditions as the primary cause of all œdemas? Second, these chemical œdemas have interesting clinical parallels. The puffiness of the eyelids, the thirst, the diminished urinary output when arsenic is pushed to the physiological limit clinically is but the counterpart of the œdema observed in frogs; and the same is true of poisoning by certain other metals. Similarly, the thirst after the administration of morphin, chloroform, ether or alcohol (save in small amounts), the fall in urinary secretion, the increase in the weight of the individual, and the apparent signs of œdema are again but what we observed in frogs. *All these substances make for a lack of oxygen and an ab-*

normal production of acids in the tissues. In major part, their effects are therefore to be explained through this action upon the tissues of the whole body. The body tissues become œdematous, and the thirst, the fall in urinary secretion, etc., are secondary to this, as we shall see in greater detail later.

3. Those Conditions which are Capable of Decreasing the Hydration of (Protein) Colloids Decrease Œdema, while Those Unable to do so do not Affect It.

In discussing the absorption of water by fibrin and gelatin we found that acids (and various other substances) increase the amount of water that may be thus absorbed, and the previous paragraphs have tried to show that œdema represents in the tissues a similar excessive hydration of certain colloids, also induced through the presence of abnormal amounts of acids (and certain other similarly acting substances). But in discussing the excessive absorption of water by protein colloids we noted that such could be reduced by various means. Thus, the great hydration induced through acids could be counteracted by salts of various kinds. In this simple observation resides a method of testing the validity of the colloid-chemical theory of œdema. Clearly, *the same conditions which have been found effective in reducing the swelling of fibrin and gelatin in acid solutions should also be found to counteract the development of œdema.* The following experimental observations show this to be true, and thus furnish a scientific foundation for a therapy of œdema. We became familiar above with the fact that a circulation is unnecessary for the development of most intense grades of œdema. We found that frogs' legs which had been ligated, cut from the body, and placed in a little water, developed an œdema which mimics in every way the worst types observed clinically. We will use the œdemas developed in this way in amputated frogs' legs as one type upon which to analyze further the nature of the phenomenon.

(*a* and *b*) It will first be well to get some conception of the rate of water absorption (rate of œdema development) in such frogs' (Rana) legs. Fig. 97 has been introduced for this purpose. The preparations for the experiments were obtained by throwing a loose ligature about the hind legs of frogs just above

the knee and amputating them, provision being made for a cuff of skin which could be pulled over the femoral stump before the ligature was finally drawn taut. In this way any leakage of

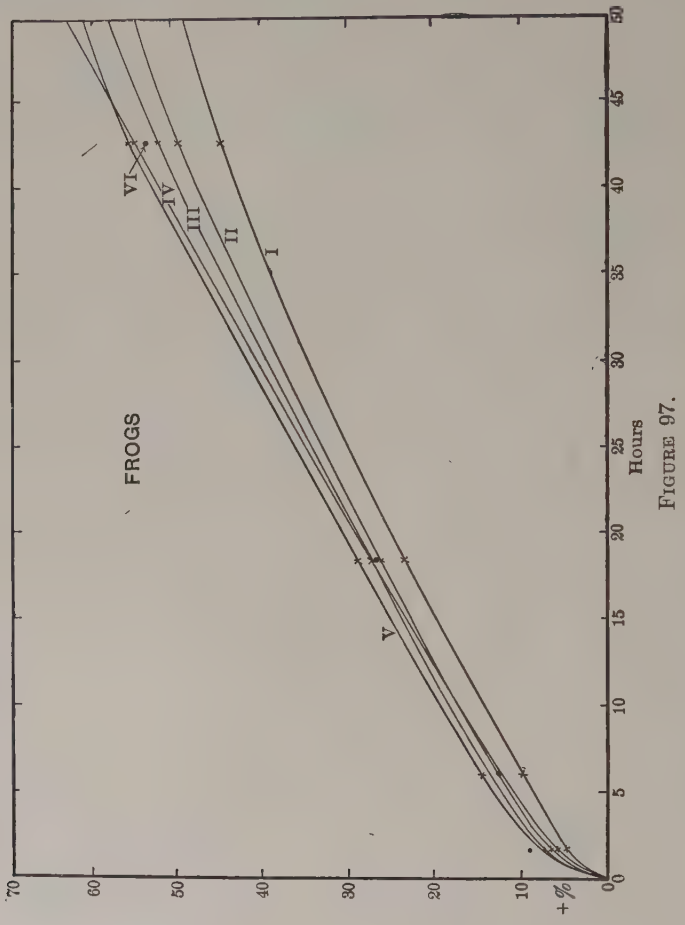


FIGURE 97.

absorbed water through the cut end of muscle, tendons, or bone at the point of amputation was avoided.

The steady increase in weight of the amputated frogs' legs is readily apparent from the figure and from Table LXXIX, which contains the experimental data. The increase in weight does not go on indefinitely. It not only ceases after a time, but an

actual loss of water ensues. We noted the same to be true in the experiments on muscle. The cause for this secondary drop is not yet clear. An actual loss of muscle substance through "solution" in the surrounding medium plays a partial rôle. I imagined that autolytic changes whereby the hydrophilic muscle colloids are broken down into substances not colloid in character might account for some of the subsequent loss. While this may play a rôle, experiment seems to indicate that it cannot be a great one. A series of tree-toad legs (muscles only) which I prepared aseptically and allowed to remain at body temperature in a moist chamber for various periods of time showed even at the end of a week the same absorption curve that the fresh muscle shows. I have come to conclude, in consequence, that the secondary loss of water occurs after the acid formed in the muscle has

TABLE LXXIX

FROGS' LEGS

Hours in the solution.	110 cc. H_2O.	110 cc. H_2O.	110 cc. H_2O.
	%	%	%
0	3.66 (0)	3.34 (0)	3.01 (0)
1.45	3.84 (+ 4.9)	3.56 (+ 6.5)	3.24 (+ 7.6)
6.00	4.00 (+ 9.3)	3.77 (+12.8)	3.38 (+12.2)
18.25	4.52 (+23.4)	4.22 (+26.3)	3.83 (+27.2)
42.30	5.33 (+45.6)	5.03 (+50.6)	4.60 (+52.8)
51.45	5.52 (+50.8)	5.22 (+56.3)	4.84 (+60.8)
68.15	5.49 (+50.0)	5.34 (+59.8)	4.98 (+65.4)
76.45	5.56 (+51.9)	5.39 (+61.3)	4.86 (+61.4)
90.30	5.64 (+54.1)	5.32 (+59.3)	4.84 (+60.8)
124.45	4.96 (+35.5)	4.78 (+43.1)	4.54 (+50.8)
	(a)	(a)	(b)
	I	II	III

Hours in the solution.	110 cc. H_2O.	110 cc. H_2O.	110 cc. H_2O.
	%	%	%
0	2.925 (0)	3.555 (0)	3.145 (0)
1.45	3.09 (+ 5.6)	3.82 (+ 7.4)	3.31 (+ 8.4)
6.00	3.28 (+12.1)	4.06 (+14.2)	3.53 (+12.5)
18.25	3.73 (+27.5)	4.59 (+29.1)	4.01 (+27.0)
42.30	4.55 (+55.5)	5.55 (+56.1)	4.85 (+54.2)
51.45	4.84 (+65.4)	5.76 (+62.0)	5.22 (+63.5)
68.15	5.17 (+76.7)	5.75 (+61.7)	5.54 (+76.1)
76.45	4.99 (+70.6)	5.80 (+63.1)	5.48 (+74.2)
90.30	5.00 (+70.9)	5.87 (+65.1)	5.50 (+74.9)
124.45	4.08 (+39.4)	5.17 (+45.4)	4.71 (+49.7)
	(b)	(c)	(c)
	IV	V	VI

reached a certain concentration, or has acted upon the tissue colloids for a certain length of time, or both, and that the loss of water is associated with a change in the colloids (denaturation?) whereby these are changed from such as have hydrophilic characteristics into such as have more decided hydrophobic characteristics.

Since the formation of acid in tissues deprived of a circulation is a firmly established fact—a fact which in these amputated frogs' legs can be verified through mere application of an indicator—we have no difficulty in interpreting these experiments by saying that *the amputated frogs' legs swell in water because the hydration capacity of their colloids is increased through the production in them of acid. The frogs' legs become œdematous for the same reason that fibrin swells more in a dilute acid than in pure water.*

(*c*) If instead of being placed in distilled water the amputated

TABLE LXXX

FROGS' LEGS

Hours in the solution.	110 cc. H_2O.	10 cc. m/1 NaCl + 100 cc. H_2O.	15 cc. m/1 NaCl + 95 cc. H_2O.
	%	%	%
0	3.42 (0)	3.42 (0)	3.055 (0)
1.25	3.55 (+ 3.8)	3.48 (+ 1.7)	3.065 (+ 0.3)
4.40	3.74 (+ 9.3)	3.59 (+ 4.9)	3.09 (+ 1.1)
21.15	4.41 (+28.9)	4.02 (+17.5)	3.37 (+10.3)
29.15	4.71 (+37.7)	4.19 (+22.5)	3.52 (+15.4)
43.00	5.03 (+47.0)	4.49 (+31.2)	3.74 (+22.4)
77.15	5.00 (+46.1)	4.95 (+44.7)	4.19 (+36.1)
96.15	4.32 (+26.3)	4.83 (+41.2)	3.98 (+30.2)
	(a)	(a)	(b)
		I	II

Hours in the solution.	20 cc. m/1 NaCl + 90 cc. H_2O.	25 cc. m/1 NaCl + 85 cc. H_2O.	30 cc. m/1 NaCl + 80 cc. H_2O.
	%	%	%
0	2.95 (0)	2.87 (0)	2.85 (0)
1.25	2.93 (− 0.7)	2.81 (− 2.1)	2.77 (− 2.8)
4.40	2.87 (− 2.6)	2.74 (− 4.5)	2.68 (− 5.9)
21.15	2.93 (− 0.7)	2.69 (− 6.3)	2.59 (− 9.1)
29.15	3.01 (+ 2.0)	2.73 (− 4.9)	2.63 (− 7.7)
43.00	3.18 (+ 7.7)	2.95 (+ 2.8)	2.91 (+ 2.1)
77.15	3.63 (+26.0)	3.49 (+21.6)	3.53 (+23.8)
96.15	3.36 (+14.2)	3.53 (+23.0)	3.50 (+22.8)
	(b)	(c)	(c)
	III	IV	V

frogs' legs are dropped *into any salt solution, they swell less than in distilled water. The higher the concentration of the salt, the less will the frogs' legs swell.* These statements are entirely analogous to those made regarding the swelling of protein colloids

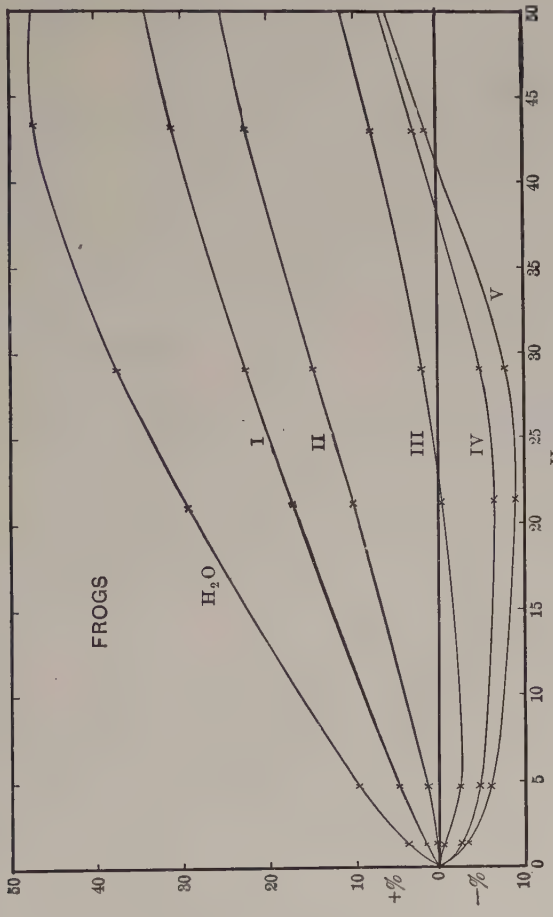


FIGURE 98.

in dilute acid solutions, and are illustrated in Figs. 98, 99, 100, and 101.

In Fig. 98, based on the experimental findings contained in Table LXXX, the curves for the swelling of the amputated frogs' legs lie progressively lower with every increase in the concentration of the sodium chlorid.

(d) When the effect of equimolar salt solutions on the swelling of amputated frogs' legs is compared, it is found that some allow

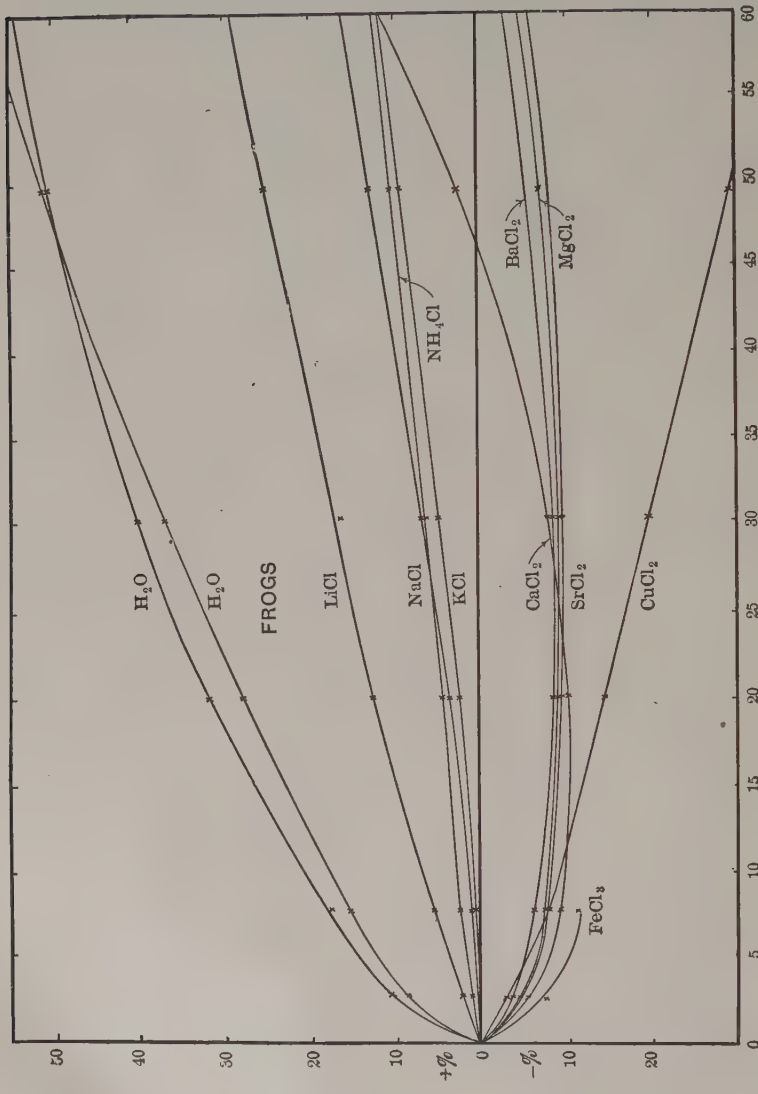


FIGURE 99.

a greater swelling than others. This is shown in Figs. 99, 100, and 101.

The action of a series of chlorids is shown in Fig. 99. We have no difficulty in recognizing the following general grouping of the basic radicals in which that least effective in preventing the swelling is placed first:

Lithium

Sodium
Ammonium
Potassium

Calcium
Barium
Magnesium
Strontium

Copper (ic)
Iron (ic)

The general grouping of these basic radicals is identical with that given for their effect on the swelling of fibrin (also gelatin gluten, aleuronat, muscle, eyes and nervous tissue) in the presence of acid.

Fig. 100 allows the comparison of a number of sodium salts.

The various acid radicals arrange themselves in the following order, that least effective in preventing the swelling being placed first:

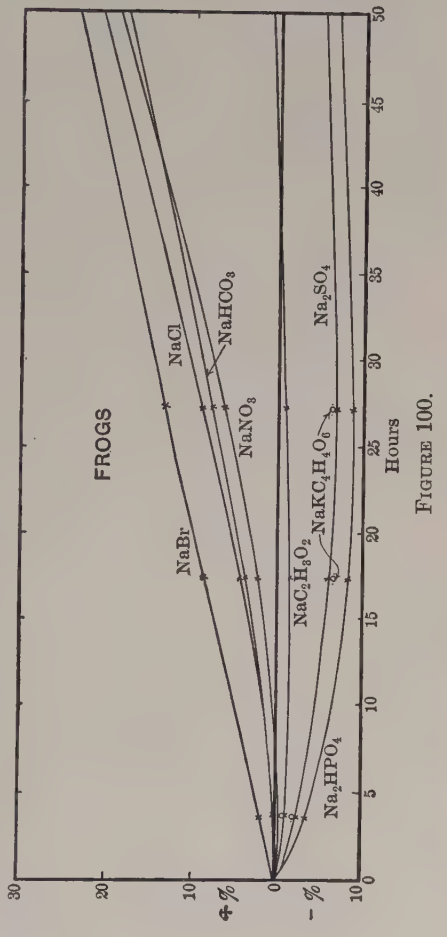


FIGURE 100.

Bromid
Chlorid
Bicarbonate
Nitrate
Acetate
Sulphate
Tartrate
Phosphate

The order is practically identical with that given for the relative effect of different acid radicals on the swelling of protein colloids in the presence of acid.

Fig. 101 shows the curves obtained with a series of potassium salts. The acetate and nitrate curves lie somewhat high. Other-

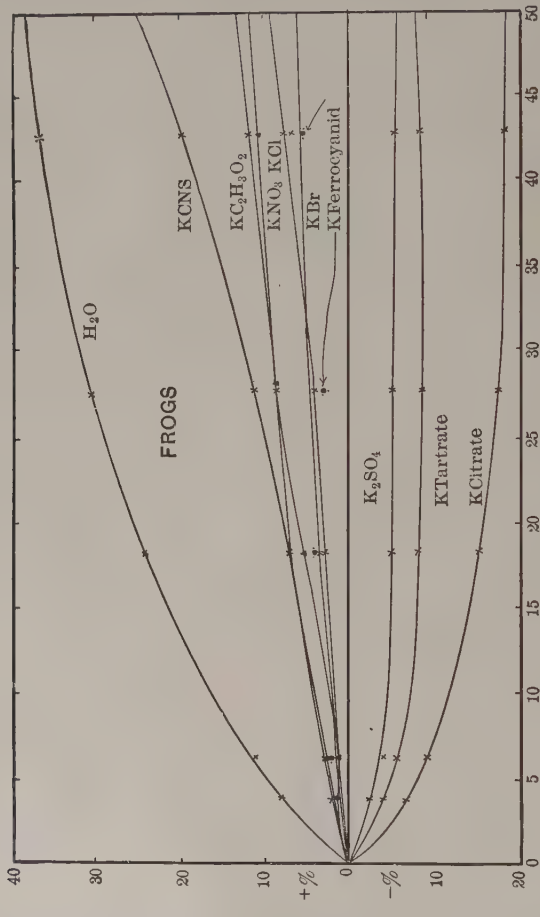


FIGURE 101.

wise the order is the same as already given for the sodium salts. Of much interest is the great inhibition in swelling induced by the citrate solution, in which the frog leg loses most heavily.

The experimental data from which Figs. 99, 100, and 101 are constructed are contained in Tables LXXXI, LXXXII, and LXXXIII

TABLE LXXXI

Frogs' Legs

Hours in the solution.	110 cc. H_2O.	15 cc. m/1 ammonium chlorid +95 cc. H_2O.	15 cc. m/1 barium chlorid + 95 cc. H_2O.	15 cc. m/1 cupric chlorid +95 cc. H_2O.	15 cc. m/1 ferric chlorid +95 cc. H_2O.	15 cc. m/1 calcium chlorid +95 cc. H_2O.
	%	%	%	%	%	%
0	2.45 (0)	2.38 (0)	2.91 (0)	2.82 (0)	3.59 (0)	2.70 (0)
2.35	2.71 (+10.9)	2.40 (+ 0.8)	2.71 (−4.8)	2.73 (− 3.2)	3.30 (− 8.0)	2.54 (− 5.7)
7.35	2.87 (+17.4)	2.43 (+ 2.3)	2.68 (−7.7)	2.60 (− 7.8)	3.18 (−11.4)	2.45 (− 9.2)
20.00	3.22 (+31.6)	2.48 (+ 4.4)	2.65 (−8.6)	2.40 (−15.0)	.....	2.43 (−10.0)
30.25	3.44 (+40.4)	2.52 (+ 6.1)	2.65 (−8.6)	2.26 (−19.8)	.....	2.48 (− 8.1)
49.30	3.78 (+50.2)	2.64 (+11.2)	2.75 (−5.5)	2.00 (−29.2)	.....	2.77 (+ 2.5)

Hours in the solution.	15 cc. m/1 lithium chlorid +95 cc. H_2O.	15 cc. m/1 magnesium chlorid +95 cc. H_2O.	15 cc. m/1 potassium chlorid +95 cc. H_2O.	15 cc. m/1 sodium chlorid +95 cc. H_2O.	15 cc. m/1 strontium chlorid +95 cc. H_2O.	110 cc. H_2O.
	%	%	%	%	%	%
0	3.24 (0)	3.29 (0)	4.05 (0)	4.04 (0)	4.50 (0)	4.23 (0)
2.35	3.31 (+ 1.9)	3.18 (−3.3)	4.05 (0)	4.04 (0)	4.27 (−5.2)	4.61 (+ 8.8)
7.35	3.43 (+ 5.6)	3.08 (−6.4)	4.07 (+0.5)	4.07 (+ 0.7)	4.20 (−6.6)	4.88 (+15.2)
20.00	3.65 (+12.4)	3.01 (−8.5)	4.14 (+2.2)	4.18 (+ 3.4)	4.10 (−9.4)	5.41 (+27.7)
30.25	3.77 (+16.1)	2.98 (−9.4)	4.22 (+4.2)	4.29 (+ 6.2)	4.06 (−9.9)	5.79 (+36.1)
49.30	4.04 (+24.4)	3.04 (−7.3)	4.44 (+9.1)	4.56 (+12.8)	4.14 (−8.2)	6.39 (+51.0)

TABLE LXXXII

FROGS' LEGS

Hours in the solution.	15 cc. m/1 sodium acetate +95 cc. H_2O.	15 cc. m/1 sodium bromid +95 cc. H_2O.	15 cc. m/1 sodium bicarbonate +95 cc. H_2O.	15 cc. m/1 sodium chlorid +95 cc. H_2O.
	%	%	%	%
0	3.39 (0)	3.42 (0)	3.33 (0)	3.25 (0)
3.35	3.36 (−1.0)	3.47 (+ 1.4)	3.33 (0)	3.25 (0)
17.30	3.34 (−1.6)	3.71 (+ 8.4)	3.45 (+ 3.6)	3.37 (+ 3.7)
27.15	3.36 (−1.0)	3.86 (+13.1)	3.59 (+ 7.8)	3.53 (+ 8.6)
31.45	3.43 (+1.0)	4.24 (+24.0)	3.95 (+18.6)	3.96 (+21.8)
70.35	3.55 (+4.2)	4.46 (+30.4)	4.19 (+25.8)	4.28 (+31.6)
100.55	3.66 (+7.8)	4.70 (+37.4)	4.44 (+33.3)	3.86 (+18.7)

Hours in the solution.	15 cc. m/1 sodium nitrate +95 cc. H_2O.	15 cc. m/1 disodium hydrogen phosphate +95 cc. H_2O.	15 cc. m/1 sodium sulphate +95 cc. H_2O.	15 cc. m/1 sodium-potassium tartrate +95 cc. H_2O.
	%	%	%	%
0	3.49 (0)	3.48 (0)	3.95 (0)	3.74 (0)
3.35	3.47 (− 0.5)	3.35 (−3.7)	3.84 (−2.7)	3.64 (−2.6)
17.30	3.56 (+ 2.0)	3.18 (−8.6)	3.71 (−6.0)	3.51 (−6.1)
27.15	3.70 (+ 6.0)	3.17 (−8.8)	3.67 (−7.0)	3.49 (−6.6)
31.45	4.19 (+20.0)	3.25 (−6.6)	3.74 (−5.3)	3.53 (−5.6)
70.35	4.58 (+31.0)	3.48 (0)	3.88 (−1.7)	3.58 (−4.2)
100.55	4.33 (+24.0)	3.69 (+5.9)	4.10 (+3.7)	3.73 (−0.2)

(*e*) *The addition of various non-electrolytes does not at the same "osmotic" concentration affect the amount of water that will be absorbed by amputated frogs' legs as greatly as does the addition of electrolytes.* I have tried ethyl and methyl alcohols, urea, glycerin, dextrose and cane-sugar. Urea increases somewhat the tendency to swell. In solutions of the remaining non-electrolytes the absorption curves are almost identical with those given in Fig. 97 for absorption from distilled water.

These experiments indicate satisfactorily that the absorption of water by a whole member such as a leg is dependent upon the state of the colloids contained in it. Its normal hydration capacity is raised when acids develop in it, and as all salts counteract the effect of an acid in favoring the swelling of a (hydrophilic) protein colloid, not only according to their concentration, but also according to their chemical character, so also do they counteract the œdema of an amputated frog's leg. Non-electrolytes which are comparatively ineffective in reducing the swelling of protein colloids are also incapable of reducing the absorption of water by an amputated frog's leg.

TABLE LXXXIII

Frogs' Legs

Hours in the solution.	110 cc. H_2O.	15 cc. m/1 potassium acetate +95 cc. H_2O.	15 cc. m/1 potassium bromid +95 cc. H_2O.	15 cc. m/1 potassium chlorid +95 cc. H_2O.	15 cc. m/1 potassium citrate +95 cc. H_2O.
	%	%	%	%	%
0	3.98 (0)	4.33 (0)	3.81 (0)	4.22 (0)	3.73 (0)
4.00	4.31 (+ 8.3)	4.42 (+ 1.9)	3.86 (+1.3)	4.25 (+0.6)	3.45 (− 7.5)
6.10	4.41 (+10.8)	4.44 (+ 2.4)	3.85 (+1.1)	4.26 (+0.8)	3.38 (− 9.5)
18.10	4.92 (+23.7)	4.61 (+ 6.4)	3.92 (+3.0)	4.34 (+2.5)	3.16 (−15.4)
27.45	5.18 (+30.1)	4.70 (+ 8.3)	3.92 (+3.0)	4.39 (+3.9)	3.06 (−18.1)
42.50	5.44 (+36.7)	4.91 (+10.9)	4.06 (+6.6)	4.54 (+7.5)	3.05 (−18.2)
71.45	5.60 (+40.8)	5.00 (+15.4)	4.08 (+7.2)	4.57 (+8.3)	3.04 (−18.6)

Hours in the solution.	30 cc. m/2 potassium ferrocyanid +80 cc. H_2O.	30 cc. m/2 potassium sulphate +80 cc. H_2O.	15 cc. m/1 potassium nitrate +95 cc. H_2O.	15 cc. m/1 potassium sulphocyanate +95 cc. H_2O.	15 cc. m/1 potassium tartrate +95 cc. H_2O.
	%	%	%	%	%
0	3.84 (0)	3.02 (0)	3.36 (0)	3.80 (0)	3.63 (0)
4.00	3.89 (+1.3)	2.96 (−1.9)	3.40 (+ 1.1)	3.83 (+ 0.8)	3.49 (−3.9)
6.10	3.90 (+1.5)	2.90 (−4.1)	3.39 (+ 0.8)	3.89 (+ 2.2)	3.42 (−5.8)
18.10	3.97 (+3.3)	2.89 (−4.4)	3.53 (+ 4.9)	4.05 (+ 6.6)	3.35 (−7.6)
27.45	3.95 (+2.9)	2.88 (−4.8)	3.63 (+ 8.1)	4.20 (+10.4)	3.31 (−8.7)
42.50	4.04 (+5.2)	2.87 (−5.1)	3.72 (+10.6)	4.56 (+20.0)	3.34 (−7.9)
71.45	4.08 (+6.2)	2.84 (−5.9)	3.80 (+13.0)	4.83 (+27.1)	3.35 (−7.6)

It has been objected to these experiments that they deal with "dead" animal tissues and that in consequence the facts learned upon them may not be applied to the "living" œdemas which we encounter clinically. Absurd as is such reasoning it is easily met. *Various salts reduce the œdema produced in living frogs by any means whatsoever just as readily as they reduce the œdema observed in amputated frogs' legs.* The injection of a poison like uranyl nitrate produces in a short time a marked œdema in frogs. This can be greatly reduced in severity if the animals, instead of being kept in distilled water, are kept in various salt solutions. The following experiments serve to illustrate this fact:

EXPERIMENT 10.—Twelve frogs that have been kept in jars of tap water for several days have the urine squeezed from their bladders, are weighed, and divided into two sets of six each in such a way that the weight of any one frog in the first series is about that of a corresponding one in the second series. They are then all injected with 0.2 gram uranyl nitrate into the dorsal lymph sac and placed in separate finger bowls each containing 100 cc. distilled water in the first series and 100 cc. RINGER solution in the second. The fluid in the bowls is changed once in twenty-four hours. The changes in the weights of the frogs are indicated in the tables on page 261.

EXPERIMENT 11.—Six frogs are weighed, each injected with 0.05 gram uranyl nitrate into the dorsal lymph sac, and divided into two sets of three each. Those of the first are kept in finger bowls each containing 100 cc. water; those of the second in bowls containing 100 cc. 1/6 molar sodium chlorid solution. The changes in weight are as follows:

SERIES IN WATER

Hours.	1	2	3	Average.
0	30 %	27 %	24 %	0
18	33 (+10.0)	?	28 (+16.6)	+13.3
26	36 (+20.0)	30.5 (+12.9)	29 (+20.8)	+17.9
42	37 (+23.3)	35 (+29.6)	29.5 (+22.9)	+25.3
68	38 (+26.6)	41 (+51.8)	?	+39.2
92	39 (+30.0)	Dead	30 (+25.0)	+27.5

SERIES IN m/6 NaCl (0.975%).

Hours.	I	II	III	Average.
0	34 %	29 %	26 %	0
18	32 (− 5.8)	29 (+ 0)	26 (+ 0)	− 1.9
26	33 (− 2.9)	30 (+ 3.4)	27 (+ 3.8)	+ 1.4
42	33 (− 2.9)	31 (+ 6.8)	28 (+ 7.7)	+ 3.9
68	38 (+11.7)	33 (+13.8)	30 (+15.3)	+13.6
92	39 (+14.7)	35 (+20.7)	Dead	+17.7

SERIES IN WATER

Hours.	1	2	3	4	5	6	Average.
0	33 %	35 %	40 %	42.5 %	49 %	60 %	**0**
18.30	44 (+33.3)	42.5 (+21.4)	51.5 (+28.7)	51 (+20.0)	53.5 (+ 9.1)	66 (+10.0)	**+20.4**
40.15	48.5 (+43.9)	44 (+25.7)	56 (+40.0)	56 (+30.8)	57 (+16.3)	71 (+18.3)	**+29.1**
64.15	48 (+43.0)	Dead	56.5 (+41.2)	Dead	62 (+26.5)	77.5 (+29)	**+34.9**
88.30	Dead	.....	59 (+47.5)	.....	69 (+40.8)	83 (+38.3)	**+42.2**
			Dead	.....	Dead		

SERIES IN RINGER SOLUTION.

Hours.	I	II	III	IV	V	VI	Average.
0	33.5 %	39 %	42 %	42.5 %	52 %	65 %	**0**
18.30	38 (+13.4)	42.5 (+ 8.9)	44 (+ 4.6)	46 (+ 7.6)	54.5 (+ 4.8)	67 (+ 3.0)	**+ 7.0**
40.15	41 (+22.4)	47 (+20.5)	49 (+16.6)	51 (+20.0)	59 (+13.4)	79 (+21.5)	**+19.0**
64.15	44 (+31.3)	52 (+33.3)	55 (+30.9)	53 (+24.7)	64 (+23.0)	84 (+29.2)	**+28.7**
88.30	47 (+40.3)	52 (+33.3)	57 (+35.0)	Dead	65 (+25.0)	87 (+33.3)	**+33.6**
	Dead	.....	.....	.....	Dead		

Incidentally these experiments show that, contrary to much clinical teaching, *administration of sodium chlorid does not increase an existing œdema.* We shall have occasion to return to this question later, but we already see that sodium chlorid is no exception to the general rule that the presence of salts leads to dehydration of protein colloids.

The effect of sodium chlorid in reducing an œdema is evident to mere inspection. In Fig. 102 *a* and *b*, is shown the untreated Frog 3 of Experiment 11, photographed at the time of injection and forty-two hours later. Fig. 103, *a* and *b*, shows Frog III treated with sodium chlorid and similarly photographed.

4. On Œdema Due to Other than Acid Causes

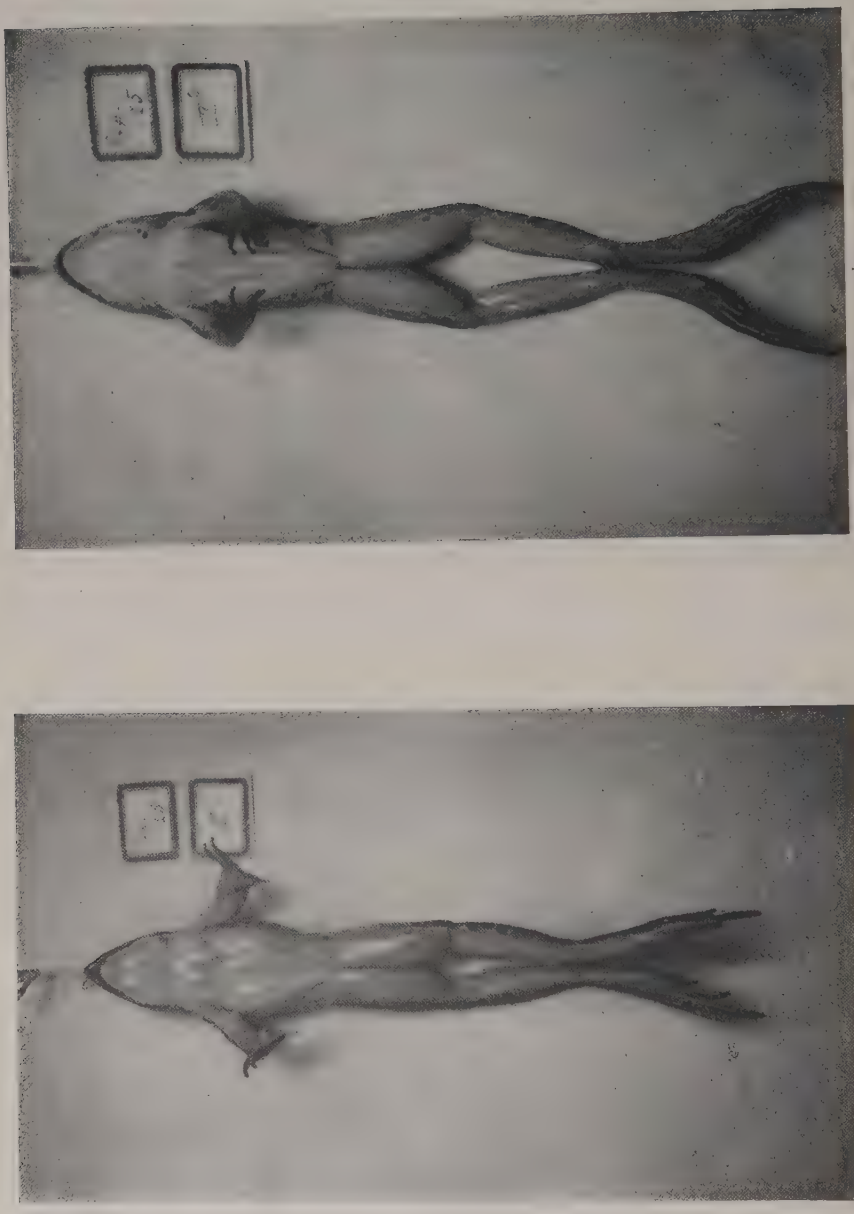
Unfavorable criticism of the colloid-chemical theory of water absorption as applied to the problem of œdema has spent its force but little upon our fundamental contention that the hydrophilic colloids and their state of increased hydration characterizes this pathological entity, but rather upon the entirely subsidiary one of the *mechanism* by which the normal hydration capacity of any hydrophilic tissue colloid is raised to the degree accepted as characteristic of "œdema." In discussing this lesser phase I have laid chief stress on the importance of an abnormal production and accumulation of acid in the affected part. My critics have for various reasons, adequate in their judgment, denied the effectiveness of this factor, but, with the exception of W. J. Gies, none has contributed any new suggestions as to what might be responsible for the increased hydration if a production or accumulation of acid were not.

Let me first reëmphasize that I have never held an acid production and accumulation to constitute, of necessity, the *only* factor responsible for the increased hydration which characterizes œdema. I pointed out even in my first papers [1] that a conversion of colloid material of one type into another more highly hydrated type might lead to œdema, and emphasized the importance of Wolfgang Ostwald's findings in this connection, according to which Beta-gelatin swells more than the ordinary kind. Since Beta-gelatin is a partly hydrolyzed one, and since this change has much in common with the first changes

[1] See the bibliography at the end of this volume.

a *b*

FIGURE 102.



b

a

FIGURE 103.

of protein digestion under the influence of proteolytic ferments, it was but natural that the possible importance of these in the production of œdema should come to mind. WILLIAM J. GIES [1] has since insisted upon this point anew. The ultimate acceptance or rejection of the importance of this element in the problem must depend upon experiment. Thus far it has not been demonstrated that the ferments play any great rôle in increasing the water content of proteins, and there are absolutely no suggestions at hand as to how in œdema the chemistry of normal cellular activity becomes so upset as to allow the ferments then to do things which they do not do normally. The quantitative experiments of GROVER TRACY, FRANK R. ELDER and WILLIAM J. GIES [2]—and such only can tell us of the relative importance of different agencies in hydrating colloids—show proteolytic ferments to increase water absorption under optimal conditions only some three to six parts, when acid alone has already made the proteins take up from seventy to eighty times their original weight. But what is of greater significance for the biological aspects of the problem are the more recent experiments of EDGAR G. MILLER, Jr., and GIES,[3] which confirm an older observation of my own [4] that tissues exposed to autolytic changes swell no more than fresh tissues subjected to the same external conditions.

Beyond this my critics have been entirely barren of suggestions regarding other agencies which in biological material might be capable of increasing its hydration capacity. In colloid chemistry we know, of course, a number which increase the hydration of protein colloids, but it is quite another matter whether these ever appear in living material in sufficient amounts or are there sufficiently active to give rise to such œdemas as are encountered clinically. The only way in which such questions can be settled is by direct animal experiments. Such are simple enough in themselves and it would seem an easy matter to determine whether or not certain substances which increase the hydration of proteins *in vitro* do this also in living

[1] WILLIAM J. GIES, Biochem. Bull. **1**, 312 (1911).

[2] GROVER TRACY and WILLIAM J. GIES: Biochem. Bull., **1**, 467 (1912); FRANK R. ELDER and GIES: ibid., **1**, 540 (1912).

[3] EDGAR G. MILLER, Jr., and WILLIAM J. GIES: Biochem. Bull., **1**, 475 (1912).

[4] See page 251; or page 111 of the first edition of Œdema.

animals. But it is not always easily proved that in the latter case the given substance did this directly, and not indirectly as by interfering with the normal oxidation chemistry of the body cells, or by interfering with normal cardiac or respiratory activity. Tentatively, however, the following facts may prove of interest in connection with the general problem of œdema production in animals by means [1] other than the introduction, production or accumulation of acids in them.

It does not surprise us that frogs develop an œdema if kept in solutions containing *alkali* in toxic amounts. Alkali effectively hydrates protein *in vitro* and it does this *in vivo*. To shut out the factor of acid production (through muscular work) consequent upon the movements of the frog in the alkaline solution it is well to destroy the brain.

The accumulation of *urea* (and other nitrogenous products) in the blood and tissues of patients likely to show œdema (as in the nephritides) and its proved capacity of increasing the hydration of protein, suggested that an accumulation of urea might be one of the factors in determining the development of œdema in certain clinical cases. Experiments on frogs as thus far performed do not, however, lend any support to such a conclusion. If urea is of importance in leading to a development of œdema its rôle from a *quantitative* standpoint is rather small. Its biological importance from a *qualitative* standpoint may, however, be great because of the peculiar type of hydration which it produces and because it makes proteins readily able to go into "solution."

Both *pyridin* and some of the *amins* (ethyl and diethyl amin) lead to marked œdema in frogs. The amins are peculiarly powerful in their action, exceeding both in rate of development and in the intensity of the œdema produced all alkalies of the same concentration. This observation seems to me of fundamental importance in connection with the œdemas accompanying some of the infections, for the amin character of many of the toxins is a proved matter.

The qualitative and quantitative characteristics from an œdema-producing point of view of the materials produced in any

[1] See Martin H. Fischer and Anne Sykes: Science, **38**, 486 (1913); Jour. Med. Soc., New Jersey, **11**, 116 (1914); Kolloid-Zeitschr., **14**, 215 (1914); ibid., **16**, 129 (1915).

ordinary infection are well illustrated by such analyses as those of O. EMMERLING.[1] From a culture medium of 860 grams of egg white inoculated with staphylococcus pyogenes aureus EMMERLING isolated an uncalculated amount of formic acid, 2.5 grams acetic acid, 0.6 gram propionic acid, 10.8 grams butyric acid, 0.5 gram other fatty acids, 2.0 grams oxalic acid, 0.3 gram succinic acid and 3.5 grams trimethylamin. From 600 grams moist wheat gluten inoculated with proteus vulgaris he isolated large amounts of formic, acetic and butyric acids (18 grams of the latter) as well as some of the higher fatty acids. He obtained also 0.65 gram phenol, more than 5.0 grams of ammonia[2] and appreciable quantities of trimethylamin. Aside from the fact that there is no unanimity regarding what constitutes a toxin and the further fact that the work of such men as BRIEGER shows that the staphylococci produce no substances which satisfy the qualifications of the toxins, the question may well be asked, need we have recourse to such hypothetical compounds to explain the tissue changes either locally or constitutionally produced by an infecting organism? The analyses of EMMERLING show that sufficient quantities of easily isolated and simple chemical compounds are produced in the course of the ordinary infections to account readily for even the most destructive changes observed either clinically or postmortem. The significance of such values for the understanding of the etiology, pathology and treatment of the changes incident to the infections needs no comment.

A series of important observations made by ALLAN EUSTIS[3] fit in here. EUSTIS has for several years insisted on clinical grounds, as have others, upon the importance of protein derivatives in the production of certain œdemas such as bronchial asthma and urticaria. His clinical experience has, however, been

[1] O. EMMERLING: Ber. d. deut. chem. Gesellsch., **29**, 2721 (1896).

[2] ALLAN EUSTIS has called my attention to the fact (Personal communication (1920)) that much of the so-called ammonia fraction obtained in analyses of the blood, urine and other body fluids, is probably not at all attributable to the existence of ammonia as such in these fluids, but represents ammonia produced in the process of analysis from decomposition of various amins. Considering the tremendous hydrating properties (œdema-producing properties) of the amins, it is small wonder that swelling is the commonest accompaniment of all the ordinary infections in which a decomposition of protein material occurs under the influence of pathogenic organisms in the living animal body.

[3] ALLAN EUSTIS: Am. Jour. Med. Sci., **143**, 862 (1912); New Orleans Med. and Surg. Jour., **66**, April (1914).

supported by experiment, in that he has shown that betaimidazolylethylamin (a putrefaction product of the histidin normally produced in digestion) when applied to the slightly broken skin is followed by an intense urticarial-like eruption.

IV

ON THE PASSIVE CONGESTION ŒDEMAS OF THE KIDNEY AND THE LIVER

It is our next problem to discuss some *special aspects of œdema*, in so far as such affects certain organs or constitutes the prominent feature of special pathological or clinical states. Nephritis, for example, is in good part an œdema of the kidney, glaucoma an œdema of the eye, uremia an œdema of the brain; on the other hand, a deficient urinary output, an increased intraocular tension or a coma are but the clinical parallels if not the direct expressions of these œdemas. Because of their great clinical interest, glaucoma, nephritis and uremia receive detailed discussion later. Here we want to touch upon certain other aspects of œdema not discussed there which in addition to bringing further evidence for the colloid-chemical concept of œdema serve also to illustrate how I think we must interpret, and more correctly, certain well-known and long-recognized pathological and clinical facts.

How, on the basis of the foregoing discussion, are we to understand the so-called *passive congestion œdemas of the kidneys and the liver?* In consequence of interference with the outflow of blood from these organs, be this due to a merely local disturbance, such as pressure upon the efferent vein, or to a more general one, such as heart disease, they become filled with blood and increase in size. The increase in size is independent of the presence of an excessive amount of blood in the organ; it is due, in other words, to an increase in the size of the individual cells and tissues themselves—an œdema. For this œdema of the parenchymatous organs the same factors of increased blood pressure, increased permeability of blood vessel walls, etc., that are so familiar to us from our previous considerations, have again been held responsible. In fact, the deductions made from consideration of the well-defined passive congestion œdemas of various organs as observed clinically or produced experimentally may be said to

have colored our whole conception of the essential nature of all classes of œdema.

There exists no dearth of isolated experimental and clinical observations on the passive congestion œdemas of the liver and the kidney, but the attempts that have been made to correlate them can hardly be said to have proved successful. Adherents of the pressure theory of œdema, for example, cannot meet the fact that an increase in blood pressure is all too often absent in patients with marked "congestion" of the kidneys or liver; that swollen, passively congested organs decrease in size after the use of drugs whose chief action makes for an *increase* in blood pressure; and that enormous experimental increases in blood pressure in animals do not lead to œdemas of these organs. On the other hand, believers in the increased permeability of blood vessel walls have never proved their point physico-chemically; nor have those who have recently resurrected the rôle of hydremia forty years after COHNHEIM buried it experimentally.

On the colloid-chemical basis we interpret the phenomena that characterize the passive congestion œdemas of kidneys or liver as follows: *The cause of the oedema is again to be sought in the tissues. The circulatory disturbances leading to an œdema of these organs all have this in common: they bring about a state of oxygen want in the tissues in consequence of which acids are produced in them. These increase the capacity of the tissue colloids for holding water, whereby they are enabled to absorb an increased amount from any available source.* This idea is supported by the following:

§ 1

It is a well-known fact that when the efferent (renal) vein of the kidney is tied in animals, the organ becomes filled with blood, while the kidney tissues proper swell and become progressively firmer in consistence. This is the typical picture of a passive congestion sufficiently severe to permit of the development of an œdema in the congested area. We need not repeat that what happens in this experiment is usually interpreted as an œdema due to an increased blood pressure, alterations in vascular permeability, etc. All these explanations fall as soon as it is stated that *ligation of the renal artery leads to the same series of changes in the kidney as ligation of the renal vein* (with

the exception of the overfilling of the blood vessels). (See Fig. 104.)

An abstract of a few experiments carried out with GERTRUDE MOORE [1] on rabbits may serve to illustrate this point. In a series of nine Belgian hares we ligated the left renal vein in three and the left renal artery in the remaining six. The operations were made under morphin anesthesia, and in no case consumed more

A *B*

FIGURE 104.—*A*, normal right kidney; *B*, œdematous left kidney of the same rabbit twenty-three hours after ligation of the renal artery. Experiment "IV" of May 13, 1909.

than five minutes. None of the operations was complicated by infection. At various periods after the operations the animals were killed and the two kidneys of each animal weighed. As clearly apparent from the following tables, the increase in the weight of the kidney after ligation of the artery is quite as great as after ligation of the vein. The extra amount of clotted blood found in the kidney when the veins are ligated easily accounts for the somewhat higher values found in Table LXXXIV over those found in Table LXXXV.

[1] MARTIN H. FISCHER and GERTRUDE MOORE: Kolloid-Zeitschr., **5**, 286 (1909).

TABLE LXXXIV

LIGATION OF LEFT RENAL VEIN

Rabbit.	Weight of rabbit.	Hours after ligation.	Weight of kidneys.		Gain in weight in % of normal.
			Normal.	Ligated.	
May 13, '09, "VI"....	930	19.20	4.20	7.00	66.6%
May 1, '09, "C"....	1500	22.10	7.50	12.70	69.3%
May 13, '09, "V"....	811	42.40	3.80	13.95 [1]	267.1% [1]

[1] This unusually high figure was due to the fact that an enormous extravasation of blood into the capsule with œdematous swelling occurred in this case.

TABLE LXXXV

LIGATION OF LEFT RENAL ARTERY

Rabbit.	Weight of rabbit.	Hours after ligation.	Weight of kidneys.		Gain in weight in % of normal.
			Normal.	Ligated.	
May 13, '09 "I".....	970	4.25	5.60	6.50	16.1%
May 13, '09, "III"...	1127	19.00	5.07	7.95	56.8%
May 13, '09, "IV"...	1115	23.00	4.75	7.42	56.4%
May 1, '09, "A"....	1500	23.00	7.43	11.70	57.3%
May 13, '09, "II"....	734	42.15	3.63	6.65 [1]	83.2% [1]
May 1, '09, "B"....	1560	48.00	7.40	10.65	43.9%

[1] This high value was due in part to an extravasation of blood into the capsule with œdematous swelling. Note that the escape of blood occurred after ligation of the *artery* (diapedesis without blood pressure!).

A decrease in blood pressure is, therefore, quite as effective in bringing about an œdema of the kidney as an increase. While such a result is unexplainable on the basis of the widely accepted pressure theory of œdema it is not surprising to us. In fact, such an experimental result was anticipated. Ligation of the vessel which carries the arterial blood to an organ must of necessity lead to a state of oxygen want in the tissues quite as readily as ligation of the vessel which carries the venous blood away.

We turn now to the *liver*, where, owing to the anatomical peculiarities of its vascular supply, valuable conditions are offered for experiments with which to test further this colloid conception of œdema.

The kidney is supplied with blood through the renal artery, which it will be recalled is very large as compared with the size of the organ. The physiological purpose of this anatomical arrangement is not far to seek. Through this artery there must

pass to the kidney not only enough blood to supply the kidney tissues with oxygen, but all that blood from which the kidney separates the urine. In the case of the liver the blood supply is quite different. Through the venous *portal blood* the characteristic functions of the liver are subserved; through the arterial blood furnished by the *hepatic artery* the parenchyma is supplied with its necessary oxygen. Both these streams unite to leave the liver through the *hepatic vein.*

When now a liver becomes decidedly œdematous from passive congestion, say in consequence of a heart lesion or pressure upon the hepatic vein, how is this result to be interpreted?

After our remarks on the essential rôle played by oxygen want, and not mere blood pressure changes in the production of œdema in the kidney, the well-known fact that ligation of the *portal vein* is not followed by an œdema of the *liver* does not surprise us—the portal vein carries only venous blood to the liver, and so changes in its parenchyma due to a production of acids are not to be expected. Quite a different picture is obtained when the *hepatic artery is ligated. In spite of the fall in blood pressure brought about by this means the liver rapidly develops an intense œdema.* This result is quite expected on the basis of our theory, and indicates clearly that *the real reason why a passive congestion leads to an œdema of the liver is because it interferes with the necessary flow of arterial blood through the organ via the hepatic artery.*

The following four experiments show how quickly ligation of the hepatic artery in rabbits leads to œdema of the liver, and how severe this is. The œdema follows ligation the more rapidly and is the more intense the more perfect the ligation of the various branches that constitute the hepatic artery in this animal. The operations were again made under morphin anesthesia, in ten to fifteen minutes and without infection. The increase in the size of the liver, while readily apparent to the eye, can be expressed numerically only by indirect calculation of the weight of the liver in percentage of the body weight of the operated animal. In a series of six *normal* rabbits we found the liver to constitute 2.9 per cent, 3.2 per cent, 3.5 per cent, 3.7 per cent, 3.7 per cent, and 3.7 per cent (an average of 3.45 per cent) of the total body weight. Table LXXXVI shows how much the liver is increased in size when the hepatic artery is ligated.

TABLE LXXXVI

Rabbit.	Weight of rabbit.	Hours after ligation.	Weight of liver at autopsy.	Per cent of body weight.	Remarks.
May 14, '09, "VIII"	845	13	48.5	5.7	One well-defined artery to the liver.
May 1, '09, "XX"	694	16	37.3	5.3	One well-defined artery to the liver.
May 14, '09, "IX"..	867	18	35.7	4.1	Artery has several branches, one only ligated.
May 10, '09, "Red".	764	23	33.2	4.3	Several small branches ligated.

§ 2

Having shown by these simple means that the kidneys and liver become œdematous in consequence of various circulatory disturbances only because these disturbances lead to a state of lack of oxygen in the tissues, we have now to say what are the consequences of such a state of affairs. We are especially interested in evidence which shows that under such circumstances an abnormal storage or production of acids occurs in these tissues. The accumulation of carbonic acid in the cells and tissues is a necessary consequence of any interference with the outflow of blood from (or inflow to) a part. The abnormal accumulation and production of other acids in both kidneys and liver in consequence of a disturbance in oxygen supply to these viscera has, however, been proved directly for these organs by the already quoted experiments of Trasaburo Araki [1] and Hermann Zillessen.[2] Ligation of the renal artery or vein, or ligation of the hepatic artery, is always followed by the production of lactic and other acids in the kidneys and the liver. In these acids, the (hydrophilic) protein colloids of the tissues, and an available source of water, we have, therefore, all the conditions necessary for the development of an œdema. When the renal vein is tied, the available source of water is found in the blood that attempts to enter the kidney through the renal artery and stagnates in the kidney; when the artery is tied the increased hydration capacity of the tissue colloids is satisfied by absorbing

[1] T. Araki: Zeitschr. f. physiol. chem., **15**, 335 and 346 (1891); ibid., **19**, 422 (1894). See also Hoppe-Seyler, ibid., **19**, 476 (1894).

[2] H. Zillessen: Zeitschr. f. physiol. chem., **15**, 387 (1891).

water from the blood that backs into the kidneys through the veins. In patients with passive congestion of the kidneys a ready source of water is, of course, found in such a circulation as continues through these organs. When the hepatic artery is tied, or in clinical cases of passive congestion of the liver, a plentiful source of water is found in the portal circulation and the blood from the hepatic vein.

On the basis of these colloid conceptions of water absorption we have also now no difficulty in understanding the well-known physiological fact that an accumulation of carbonic acid in the arterial blood supply to the kidney, or any interference with the normal oxygen-carrying power of the blood unaccompanied by any changes in blood pressure, leads to an increase in the size of the kidney, in other words to, an "œdema," while an abundant oxygen supply brings about the reverse result. We can also understand why the kidney enlarges in the various toxic forms of nephritis. The toxic agents—various toxins, snake venoms, cantharidins, metallic salts, etc.—all belong either directly in the group of the reducing bodies or can be shown experimentally to interfere with the normal oxidations of living cells. But interference with these oxidations is followed by the same consequences as ligation of an artery or a vein, so that a swelling of the kidney cells is a logical result. The enlargement of the liver and the kidneys in phosphorus poisoning can be explained on the same ground. The increase in the size of the liver in phosphorus poisoning is not due to an excessive deposition of fat,[1] but to an increased amount of absorbed water.

§ 3

The colloid theory seems able to harmonize satisfactorily observations which on the basis of other theories seemed contradictory, while it correlates at the same time a series of apparently unattached clinical and experimental facts. Much interest attaches itself in this connection to a series of observa-

[1] The absolute amount of fat in the liver may be actually decreased though what is present is more readily visible. See in this connection Martin H. Fischer and Marian O. Hooker: Science, **43**, 468 (1916); Kolloid-Zeitschr., **18**, 129 (1916); ibid., **18**, 242 (1916); Fats and Fatty Degeneration, 67, New York (1917).

tions by H. J. HAMBURGER [1] on the kidney and the liver; and by WAICHI HIROKAWA [2] on the kidney.

In studying the "osmotic" behavior of the kidney, HAMBURGER found all the diameters of the isolated kidney to increase when he perfused it with blood serum to which an acid had been added, and to decrease when he replaced the acid with an alkali. Isolated kidney cells behave similarly. They swell in water and in weak salt solutions. In sufficiently strong solutions of neutral salts they keep their normal size or even shrink. In these experiments the action of acids and alkalies is entirely unintelligible on the osmotic basis of water absorption, and close scrutiny reveals unexpected disparities between observed and calculated effects of the different salt solutions. Our colloid theory fares better. The perfusion with acidified serum leads to an increased hydration capacity of the tissue colloids. When the serum is alkalinized the acid present in the kidney is neutralized and through the simultaneous reduction in acidity and the production of salts in the tissues the hydration capacity of the colloids is decreased, hence shrinkage of the organ. The isolated kidney cells suffer oxygen want and become acid after removal from the body. For this reason they swell when placed in distilled water. Salt solutions counteract this swelling, and this the more the higher the concentration of the salt, as experiment proves. The whole series of phenomena is identical with that previously described in our experiments on the swelling of fibrin.

HIROKAWA also studied the "osmotic" behavior of kidney cells. He found blocks of kidney tissue progressively more capable of absorbing water from increasingly stronger solutions of sodium chlorid the longer the blocks of tissue had been out of the animal. HIROKAWA correctly attributes this finding to the postmortem production of acid in the tissues, which he believes to increase the capacity of these tissues for holding water in the same way that K. SPIRO found the capacity of gelatin plates for holding water raised through the addition of a little acid.

[1] H. J. HAMBURGER: Osmotischer Druck und Ionenlehre, **3**, 52, and ibid., 50 and 54, Wiesbaden (1904).

[2] W. HIROKAWA: Hofmeister's Beiträge z. chem. Physiologie, **11**, 458 (1908).

Kidney cells, therefore, can become "œdematous" when entirely removed from the body; in other words, when entirely away from any vestige of a circulatory system. It only remains for us to connect the behavior of these "dead" kidneys with that of the passively congested "living" ones in an animal. This is done as soon as we recall the fact that the postmortem production of acids in the tissues, and that which occurs in the absence of an adequate oxygen supply represent identical processes.

Experimental data are at hand which show that in the entire absence of any circulation, *liver* cells also may show all the signs of an œdema that we are accustomed to look for in an autopsy. H. J. HAMBURGER[1] found isolated liver cells and blocks of liver tissue to swell in water and in dilute salt solutions, and to maintain their volume or even shrink if stronger salt solutions or dilute alkalies were added. Dilute acids, including carbonic, markedly increased the swelling. These remarks again parallel the effects of acids, alkalies and salts on the swelling of fibrin or gelatin in a faintly acid solution.

V

ON THE NATURE AND CAUSE OF PULMONARY ŒDEMA

The most generally accepted explanation of pulmonary œdema is that of WILLIAM H. WELCH,[2] according to whom it is due to "a disproportion between the working power of the left ventricle and of the right ventricle of such character that, the resistance remaining the same, the left heart is unable to expel in a unit of time the same quantity of blood as the right heart." It is readily seen that this theory is a mechanical one which assumes that through a heightened pressure of blood within the pulmonary circulation fluid is squeezed into the tissues of the lung and out into the alveoli and bronchi. According to

[1] H. J. HAMBURGER: Osmotischer Druck und Ionenlehre, **3**, 40, and 54 Wiesbaden (1904).

[2] WILLIAM H. WELCH: Virchow's Arch., **72**, 375; (1878); the quotation is transcribed from a letter to S. J. MELTZER, American Medicine, **8**, 195 (1904).

this conception pulmonary œdema is placed in the general group of JULIUS COHNHEIM's [1] congestion œdemas.

WELCH's ideas have not gone unchallenged. Through the observations of various authors, particularly H. SAHLI [2] and M. LÖWIT [3] it has been proved beyond doubt that the severest grades of pulmonary œdema may exist clinically and be produced experimentally without any evidence of an increased pressure in the pulmonary circuit. WELCH's theory has in consequence been variously modified or cast aside entirely. We hear again of "increased permeability of blood vessel walls," of "hydremia," of "secretory" disturbances, of still more vague "irritations," and, when all these fail, of changes in the peculiar "life" of the cells themselves. The views held by the various authors are so divergent and at times so flatly contradictory that a detailed discussion of them is purposeless. The vagueness of these theories stands in sharp contrast to the really excellent experimental and clinical observations that are available. A unifying interpretation of these is still lacking. Toward such the following is offered:

The problem of pulmonary œdema is identical with the problem of œdema in such an organ as the liver. The reason for this is at once apparent when we call to mind that the vascular arrangement in the lungs is similar to that which we previously discussed for the liver. Just as the liver, so is the lung supplied with two blood streams—with a venous stream through the pulmonary artery, which only passes through the lung for purposes of oxygenation, and an arterial stream through branches from the thoracic aorta, the bronchial arteries, which supplies the parenchyma of the lung with oxygen. The blood brought by these nutrient arteries leaves the lung in part through the bronchial veins, in part admixed with the blood of the lesser circulation through the pulmonary veins. *The facts at hand on the experimental production of pulmonary œdema are easily interpreted by saying that an œdema results whenever the oxygen supply to the parenchyma of the lung is sufficiently interfered with.*

[1] JULIUS COHNHEIM: Allgemeine Pathologie, 2d Ed., **1**, 501, Berlin (1882).

[2] H. SAHLI: Arch. f. exp. Path. u. Pharm., **19**, 431 (1885).

[3] M. LÖWIT: Ziegler's Beiträge, **14**, 401 (1893).

If the pulmonary artery passing to one lung is ligated, no œdema results. If, in addition, most of the branches passing to the opposite lung are similarly treated, we still get no œdema. Enough circulation needs only to be maintained through the lung to keep the animal alive. This result is, to our mind, entirely to be expected, for such ligations do not interfere with the oxygen supply to the parenchyma of the lung. Ligation of the pulmonary veins may lead to œdema of the lungs, but only if sufficiently extensive to shut off most of the blood as it returns from the lung. In other words, it is not an easy matter to dam back the blood in the bronchial arteries (which discharge in part into the bronchial veins, in part into the pulmonary veins) by ligating only the pulmonary veins. These experiments show that interferences with the pulmonary circulation itself are, on the whole, scarcely able to lead to an œdema of the lung.

The most effective way to bring about a pulmonary œdema is to disturb the *systemic circulation*. Compression of the left ventricle leads to pulmonary œdema, as does ligation of the aorta either at its root or not lower than the point of origin of the left subclavian artery. Ligation of the thoracic aorta low down, or of the abdominal aorta, does not lead to pulmonary œdema. These undisputed experimental facts are hard to understand on the basis of any pressure theory. While a rise of blood pressure in the pulmonary circuit may well be present in all these experiments, why should it be *more* effective when induced through ligation of the aorta than through direct ligation of the pulmonary vein? And why should ligation of the aorta to just below the left subclavian artery lead to a pulmonary oedema, and ligation just a little lower down be ineffective? Only a few small arteries are given off by the thoracic portion of the descending aorta. We experience no difficulty in interpreting all these findings when we recall that *the bronchial arteries leave the aorta just below the left subclavian. Compression of the left ventricle and ligation of the aorta to just below the subclavian all spell a lack of oxygen for the lung parenchyma, and hence an œdema. A ligation just below the bronchial arteries is without effect in this regard.*

These experiments show that a pulmonary œdema develops under the same conditions as an œdema anywhere else—whenever the lung parenchyma is placed in a state of lack of oxygen. This

state of oxygen want we always discovered to be important in other organs because it led to an abnormal accumulation or production of acids in the tissues. That such conditions prevail when the lungs become œdematous is borne out, not only by the fact that a pulmonary œdema is never induced in any animal by the various ligations described above without gross evidences of improper aëration of the blood, but by the following facts regarding chemically induced œdemas, and the œdemas of excised lungs.

Pokrowsky, Friedländer, and Herter [1] found that rabbits and dogs which had breathed for some time an atmosphere rich in carbon dioxid showed grades of pulmonary œdema at autopsy which varied from such as were scarcely recognizable to such sufficiently intense to kill the animals. Œdemas have also been noted after inhalation of the fumes of various other acids. Other chemical methods of inducing a pulmonary œdema lead to a state of lack of oxygen and acid production in the tissues in a more indirect way. Under this heading come hydrocyanic acid, various ethers and anesthetics, carbon monoxid, adrenalin, and iodin—all of them substances which we know interfere markedly with the normal oxidations of living cells.

The clinical evidence that pulmonary œdema is more often an accompaniment of the œdema of nephritis than of the œdema of heart disease is also easily understood on the basis of this chemical origin of pulmonary œdema. In nephritis we have the toxic bodies which are responsible for the œdema of the kidney more or less uniformly distributed throughout all the tissues of the body. The parenchyma of the lungs is therefore as likely to be affected by these toxic bodies as the parenchyma of any other organ.[2] In heart disease, on the other hand, the severity of the œdema of any organ is distinctly dependent upon the quality of the circulation going through this organ which in turn determines the amount of oxygen furnished the organ and the readiness with which the carbonic acid formed in it is carried away. Generally speaking, the greater the distance of an organ from the left ven-

[1] Cited from Cohnheim, Allgemeine Pathologie, 2d Ed., **1**, 502, and **2**, 273, Berlin (1882).

[2] The pulmonary œdemas seen in patients with blood vessel disease are not at once to be attributed to a "nephritis" which they may show. They are more commonly the direct consequence of *vascular disease involving the bronchial arteries.*

tricle, the poorer must be its oxygen supply, and in consequence the greater its opportunity to develop an œdema. In heart disease the lung is, therefore, of all the organs, in the best position to be supplied even to the last, not only with the best oxygenated blood available, but with that lowest in carbonic acid. This explains why, in spite of much embarrassment in the pulmonary circulation, an œdema of the lung need not develop. It does not until the lung parenchyma itself suffers from lack of oxygen, a state not reached until an inadequate amount of blood, or an inadequately aërated one is supplied through the bronchial arteries. Hence the so common *terminal* pulmonary œdema. Cohnheim has well said, "man does not die because he develops a pulmonary œdema, he develops a pulmonary œdema because he is dying." The gradually developing lack of oxygen and the accumulation of carbonic acid in the lungs in consequence of a gradually failing circulation and respiration account for it without difficulty.

This conception of pulmonary œdema can be tested in yet another way. If the lung becomes œdematous from any condition which interferes with a normal oxygen supply to the parenchyma, then it ought to be particularly easy to produce an œdema in a lung when removed from the body. The *most intense œdemas which simulate in every way those observed at the autopsy table may be produced in lungs removed from the body, and in the entire absence of any such blood pressures as are considered active in the current theories of pulmonary œdema.*

The entire uninjured lungs of sheep freshly obtained from a nearby slaughter house, and with the heart intact, served for material in these experiments. As injection fluids, I used water, various salt solutions, dilute acids, and these mixed with salts. As the experiments are incomplete I describe only the effects of injecting water or m/6 (0.975%) sodium chlorid solution into the pulmonary arteries. With use of either of these fluids an intense pulmonary œdema results. The experiments are carried out in the following way: A cannula is first tied into the pulmonary artery; a ligature is next thrown about the heart below the cannula, and the heart cut off below this ligature. After adherent tags of tissue are removed, the lung is weighed and hung up by a ligature drawn through the trachea. If, now, a sodium chlorid solution or distilled water is simply allowed to *trickle* into a funnel

connected with the glass cannula inserted into the pulmonary artery, the lung takes up enormous amounts of the fluid in a very short time. A lung weighing 500 grams will take up two to three liters of either of these fluids in an hour or two. What becomes of them is interesting. The lung tissue itself is first affected. It swells up enormously (more than doubling in weight after infusion for an hour or two), and in the earlier periods of the experiment, if the influx of fluid into the pulmonary artery is stopped, the lung may be turned upside down and not a drop of fluid flow out of either the blood vessels or the trachea. If the injection of fluid is continued the pleural surface after a time becomes moist, and soon a drop of fluid falls from the lower edge of the lung. This is soon followed by another and another until a steady drip is established which may amount to several hundred cubic centimeters of "pleural exudate" in the course of an hour. At the same time the lung can no longer be turned upside down without obtaining a bloody, frothy fluid from the trachea. This fluid gradually rises in the trachea, and if not removed, overflows. The overflow continues as long as the infusion of water or salt solution into the pulmonary artery is kept up (several hours). Let it be noted that all this time not a drop of fluid comes out of the veins, even though these have not been ligated. *If the infusion is properly regulated the tissues take up all the fluid that passes into the artery, absorb much of it themselves, and then allow it to pass over into the alveoli and bronchi and through the pleura.* Even after the infusion of liquid has been kept up for several hours, only a few cubic centimeters can be recovered from the blood vessels.

From the experiments that have been carried out thus far it may be said that the longer the lungs have been out of the animal, the more quickly do these signs of a pulmonary œdema develop. Of the various injection fluids used, water leads to the greatest œdema of the parenchyma of the lung itself. When any salt solution is used this is not so great, but the evidence of fluid in the bronchi is obtained earlier, and this "secretion" is more intense. Sodium citrate and sodium sulphate are more powerful in this regard than sodium chlorid. In other words, the salts which dehydrate various protein colloids most are also most powerful in dehydrating the pulmonary tissues, and thus of permitting the greatest accumulations of fluid in the alveoli.

We have thus far spoken of pulmonary œdema as a pathological entity in the sense in which this term is ordinarily used in pathology. But for purposes of discussion and for the ultimate solution of the problem I believe that *we will have to distinguish between the mere presence of an increased amount of fluid in the tissues of the lung proper, and the presence of fluid in the alveoli.* While in the ordinary pulmonary œdema evidence of both is found, greatest weight is usually laid on the occurrence of fluid in the alveoli and bronchi. When this is present it undoubtedly represents the extreme of what we are pleased to call a pulmonary œdema. But very severe œdemas of the lung may exist without any fluid in the alveoli (as in the earlier periods of the œdemas produced in excised lungs). The presence of an excessive amount of fluid in the lung tissues proper and the presence of abnormal amounts of fluid in the alveoli are rather to be regarded as associated, though not identical processes. *We have no difficulty in interpreting all the phenomena of the œdema of the lung tissue itself on the basis of our colloid theory of water absorption.* The tissues of the lung in pulmonary œdema come to hold an increased amount of water because acids are produced in them. Whether the possibilities for such an abnormal accumulation of acid are offered the lung by ligating various blood vessels in the body or by taking it out of the body is immaterial. That water absorption really represents but an excessive hydration of certain protein colloids is again proved by the fact that all salt solutions inhibit the development of the œdema of the lung tissues proper, not only according to the concentration of the salt employed, but according to the character of the salt. The citrate and sulphate of sodium, for example, inhibit the absorption of water by the lung tissues themselves *more* than the chlorid. Yet just the reverse holds regarding the giving off of fluid into the bronchi. The explanation of the mechanism by which this water is given off is discussed, in part in the next paragraphs which consider syneresis in colloids, in part in later chapters dealing with secretion. Why the different salts behave as they do we shall learn there.

VI

SYNERESIS AND THE ACCUMULATION OF FLUID IN THE BODY CAVITIES IN ŒDEMA

As familiarly known, it is characteristic of the œdemas occurring in the higher animals, for fluid to accumulate in the body cavities. In the œdemas of heart disease, for example, we observe not only excessive quantities of fluid in the tissues themselves, but the pleural, pericardial and peritoneal cavities come to contain an abnormally great amount. This fluid is not water, but a colloid solution in which the proteins appear in lower concentration than in the normal body fluids (blood and lymph). Similar serous accumulations occur within the tissues themselves. It is generally said that a "transudation" of fluid occurs into the tissue spaces, such a space being regarded by many as a kind of miniature serous cavity. In truth no such cavities of course, exist; they are made by the serous fluid as this separates from the more solid (œdematous) tissues. How are these accumulations of fluid brought about?

The explanation has been given by Wolfgang Ostwald [1] in directing attention to the syneresis exhibited by colloids. As first noted by Thomas Graham, hydrated colloids which were previously "dry" separate off liquid on standing. The separated fluid is not the pure solvent, but a dilute solution of the colloid. The classic example of this sort of change is seen in Fig. 105, where a silicic acid gel which originally showed no free fluid has, on standing, liberated the large amount shown in the photograph. In doing so the originally more highly swollen gel shrinks, as indicated by the space between the edge of the solid colloid and the flask. What is important to us biologically is that proteins show the same type of change. Solid gelatin as well as other protein media, as the familiar blood serum of the bacteriologists, all squeeze off fluid containing protein on standing. The bacteriologists call this "water of condensation," but this is incorrect, for the fluid is really squeezed out by the protein. The more highly hydrated the protein colloid, the more fluid is squeezed off. This is shown in Fig. 106. Each of the flasks from left to right contains respectively 200 cc. of a 5, 4, 3, and

[1] Wolfgang Ostwald: Personal communication (1913).

2 per cent solid gelatin. The photograph was taken after the flasks had stood for $2\frac{1}{2}$ days in an ice chest. Separation of a dilute gelatin solution is evident in the flask on the extreme

FIGURE 105.

FIGURE 106.

right and some has been freed in the flask next to it. No separation of liquid occurred in the more concentrated gelatin contained in the two flasks on the left.

The accumulation of fluid in the serous cavities and in the so-called tissue spaces in œdematous states represents the separation of a dilute liquid protein colloid from the more solid, heavily hydrated ones making up the œdematous tissues themselves. It is the analog of syneresis as observable in hydrated colloids. As degree of hydration and the time element are of importance in determining the amount of fluid that is thus squeezed off from laboratory colloids, so also do the high hydration characteristic of œdema and the time element, as determined by the chronicity of the agencies leading to the œdema, play important parts in the development of its accompanying "transudations."

Incidentally, these remarks may suffice to answer the criticism first raised by W. J. Gies [1] and more recently repeated by Felix Marchand,[2] Rudolf Klemensiewicz,[3] C. Ziegler [4] and others according to which the colloid-chemical theory of œdema is inadequate because there is nothing in the behavior of colloids to explain the mechanism of "transudation."

VII

CONCLUDING REMARKS

It would be a task of purposeless length to review the myriad contributions of various authors to the facts and theories of œdema and attempt their reinterpretation in the terms of colloid chemistry. To satisfy some of my critics who insist on such kindergarten methods it may suffice to indicate the road which any such reinterpretation must follow.

Suppose we choose for comment so simple a fact as that the injection of large quantities of "physiological" sodium chlorid solution is likely to be followed by some œdema in an animal. Does this prove that "increased blood pressure," "plethora"

[1] W. J. Gies: Biochem. Bull., **1**, 124 and 279 (1911 and 1912); other criticisms by Gies as well as my answers to them (ibid., **1**, 444 (1912)), are also found here. See also F. G. Goodridge and W. J. Gies: Proc. Soc. Exp. Biol. and Med., **8**, 106 (1911), and my answer in the first edition of my "Nephritis" (page 184).

[2] F. Marchand: Verh. d. neut. Naturforsch. u. Ärzte (1912).

[3] Rudolf Klemensiewicz: Verh. d. deut. Naturforsch. u. Ärzte (1912); see also, M. Körner: Transfusion, newly edited by Klemensiewicz, Leipzig (1913), where the latter's criticisms are stated more moderately.

[4] C. Ziegler: Verh. d. deut. Naturforsch. u. Ärtze (1912).

and "hydremia" are the cause of œdema, as some insist to this day, forty years after COHNHEIM and LICHTHEIM and their followers showed that no reasonable amount of injected fluid ever did this? I think not.

In a long series of experiments on rabbits, made with an entirely different object in view, I found it necessary to inject intravenously such amounts of sodium chlorid solution as were used by these authors. I found invariably that if the injections were only continued *long enough* the rabbits always developed intense general œdemas. The œdema is in other words more a function of the time than of the amount of fluid injected. How are these œdemas to be interpreted? Simply by noting this: *Rabbits subjected to such prolonged and great sodium chlorid injections suffer from lack of oxygen.* In the later hours of the experiments this becomes so great that the animals are distinctly cyanotic. As soon as we have such a state of lack of oxygen we have the conditions at hand that increase the capacity of the tissue colloids for holding water, as our previously detailed experiments have shown, and so they are in a position to absorb water from the circulating liquid in the blood and lymph vessels.

Just why in such experimentally induced œdemas, the abdominal organs, for example, should develop the œdema sooner than the subcutaneous tissues is a matter that needs separate investigation. Predilection for certain regions of the body is characteristic also of various clinical forms of œdema (œdema of nephritis, œdema of heart disease). The colloids of different tissues are different, the demand for oxygen is greater in the glandular organs than in the connective tissues, etc. Just *how* the sodium chlorid injections produce the lack of oxygen also needs analysis. Simple dilution of the blood, the increased work thrown on the heart in pumping this blood, that thrown on the various glandular organs in separating the salt solution from what is the normal blood, the effect on respiration, etc., all have to be considered.

Another fact is constantly overlooked in experiments on œdema made on the higher animals—the necessity of furnishing an adequate supply of water to the tissues. This is not easily controlled in mammals, and it is for this reason that I chose to do most of my experimenting with frogs, which may be dropped into water and so be allowed to absorb all they can

take up through the skin. As mammals cannot be relied upon to drink voluntarily as much water as we might like to have them consume, one is always in the predicament of wondering just how much water ought to be injected through the stomach tube, and in experiments in which only one part of an animal is supposed to become œdematous, an inadequate water supply means too often that the affected part, in order to become œdematous, must first rob some other tissue with a lesser affinity for water before it can satisfy its own needs. After our remarks on the rôle of the colloids in œdema, it is, of course, self-evident that the over-consumption of water could not increase an œdema after the capacity of the tissue colloids for holding such has once been satisfied.

There is also no difficulty in understanding why COHNHEIM'S experiments, in which he combined the infusion of sodium chlorid solution with moderate injury to a part, always led to the development of an œdema in the part more promptly than infusion alone. The moderate injury (heat, sunburn, iodin application), simply brought about by indirect means, the so necessary change in the colloids of the tissues, and the increased capacity for holding water once established, the water of the sodium chlorid infusion quickly satisfied it. The increased swelling of protoplasm after mechanical injury, for example, goes down into the very elements of living matter. No more brilliant proof of this can be furnished than the observation of G. L. KITE [1] who found an immediate localized swelling (œdema) to follow the track of his glass needles when pushed into the protoplasm of isolated living cells when observed under the highest powers of the microscope.

The interpretation of another experimental observation of COHNHEIM [2] seems to me to need revision. COHNHEIM found that an animal which had been bled repeatedly, and injected after each bleeding with a sodium chlorid solution, finally developed a general œdema, and interpreted this as an œdema of cachexia, caused through an increased permeability of the blood vessel walls, determined primarily through a hydremia. Would it not be simpler to say that through these frequent

[1] G. L. KITE, Personal communication (1913).

[2] J. COHNHEIM: Allgemeine Pathologie, 2nd Edition, **1**, 498, Berlin, (1882.)

bleedings the animal became anemic—that is to say, its organs got into a state of lack of oxygen—and when a supply of water was furnished the tissues, whether through a sodium chlorid infusion, or in any other way, they took this up?

We need not further discuss the inadequacy of all blood or lymph pressure theories of œdema. While COHNHEIM regarded blood pressure as one of the two great factors concerned in the production of œdema, he also recognized that severe œdemas occur when no change whatsoever in blood pressure is apparent. To account for them under such circumstances he had recourse to an "increased permeability of the blood vessel walls." If in the light of modern physico-chemical conceptions we try to say just what is meant by this, we have to define the blood vessel wall as a colloid membrane. From physico-chemical observations we know that the permeability of such colloid membranes is alterable, so this far COHNHEIM is on safe ground. But of what consequence would an increased permeability of the blood vessels be from a pathological standpoint? To force liquids through the blood vessel walls is not to force them into the tissues. And the fluid of an œdematous tissue is very decidedly in the cells themselves. COHNHEIM'S hypothesis would simply squeeze the œdema fluid as far as the outer walls of the capillaries. If we try to aid COHNHEIM'S conception of permeability and make it extend to all protoplasm, then we get the cause of œdema right where we have tried to say it is, namely, in the tissues themselves; and then our problem is simply that of how tissues hold their water. In this the forces that have been suggested as active—not only the variable hydration capacity of colloids, but even the previously suggested one of osmotic pressure, with or without OVERTON'S conception of lipoid surface layers—are so infinitely greater than the highest grades of blood pressure that pathologists have ever registered that the two cannot be compared.

The more recent experiments of MAGNUS have added much to our knowledge of the *experimental* side of œdema. His results, too, are usually interpreted as lending support to COHNHEIM'S conception of the increased permeability of blood vessel walls as a factor in the production of œdema. How well they support the belief that the cause of œdema is to be sought in a change in the colloid constitution of the tissues is readily evidenced by

the following. MAGNUS found that animals which are transfused *after death* always develop a general anasarca. Living animals do not do so as readily, but they do if deeply chloroformed or etherized or injected with arsenic. In place of these words we could write, *placed in a condition of lack of oxygen with an adequate supply of water.*

With these remarks, which have been introduced simply to illustrate how I think the experimental results of the score of workers who have busied themselves with this problem of œdema should be interpreted, we will close our discussion. It is readily apparent that through experimental analysis the part played by the blood and the lymph circulations has gradually become less prominent. From having been looked upon as alone determining the amount of water held by the tissues, we have come to find that the tissues are largely their own masters in this regard. *The blood and lymph circulations carry fluid to the tissues and away from them, but what the tissues will take up or give off rests with them. Only as these circulatory systems carry to the tissues substances which directly threaten their existence, or fail to remove such as the tissues have produced, which if allowed to accumulate will overcome them, only in so far are the circulatory systems masters of the tissues.*

PART FOUR

ABSORPTION AND SECRETION IN THE COMPLEX ORGANISM

PART FOUR

ABSORPTION AND SECRETION IN THE COMPLEX ORGANISM

I

THE GENERAL PROBLEM

The previous pages have dealt with the absorption and secretion of water from the point of view of the isolated cell, tissue, or organ. Our general conclusion has been that the tissues simply soak up a certain amount of water from the fluid medium in which they lie (the blood and lymph in the case of the higher animals), and that this amount is determined by the state of the colloids found in the tissues. Before we can advantageously proceed with a discussion of the special aspects of œdema we need to consider this problem of absorption and secretion from the viewpoint of the organism as a whole. How can we utilize the teachings of colloid-chemistry in this direction?

The absorption and secretion of water by a multicellular organism seems at first sight to be decidedly different from the absorption and secretion of water as observed in a single cell—say an ameba or a muscle cell. It is easy to think of an ameba as a spherical mass of colloid material saturated with water, and under changes in its physico-chemical surroundings or through direct changes in its own chemical composition so altering this colloid material as to make it take up or give off water. As I view it, this simple conception does constitute the heart of the entire problem of water absorption and secretion as observed in this animal.

But in a multicellular organism biological facts confront us which do not at first seem to be interpretable on any such simple basis. In the mammal, for example, we find whole organs set apart, seemingly endowed with powers of absorption only, while others function seemingly only as secretory organs. It becomes hard, for example, to see just what relationship exists between a mucosal cell of the small intestine concerned almost exclusively with an absorption of water from the lumen of the gut, or a kidney cell concerned equally exclusively with a secretion of urine, and the ameba or muscle cell which now absorbs and now secretes water either in response to its own physiological demands or under the conditions with which experimentally we are pleased to surround it. And yet on closer analysis the difference between the two is not so striking.

First of all, we need to appreciate that the mucosal cell is an absorbing cell only so long as we look at it from the side of the lumen of the gut. If we regard it from the blood vessel side, the mucosal cell is a secreting cell, for what it absorbs from the gut it gives up to the blood. Similarly, the kidney cell is a secreting cell only because we usually look at it from the point of view of being a producer of urine—as a matter of fact, everything that goes to make up the normal urine was absorbed from the blood. But even if we look at the matter from the narrower point of view, the intestinal cells under certain circumstances become secreting cells in that they secrete substances into the lumen of the intestine; and according to the judgment of some authors, certain kidney cells may reabsorb materials that have been secreted by others. In essence, therefore, secretion and absorption in the higher animals is not different from absorption and secretion as observed in an ameba or any isolated tissue cell. *That which remains, therefore, to characterize absorption and secretion in the higher animals is merely this, that under normal circumstances and viewed from the point of view of the organism as a whole, absorption and secretion occur predominantly in one direction.* What requires special analysis in the higher animals is, therefore, not absorption and secretion *per se*, but the conditions existing in the multicellular organism which make it possible for certain organs to act chiefly as absorbing systems, while others act predominantly as secreting systems. This is what creates all the problems that are conveniently grouped

under the general heading of the *special physiology* of absorption and secretion, as observed in the higher animals.

Let us see, first of all, if we cannot define in general terms what must be the conditions which lie at the bottom of this predominant functioning of certain cells and tissues in one direction, and this on the basis of our belief that the colloid constitution of the living cell is primarily responsible for the phenomena of water absorption and secretion by the cell.

An ameba or an isolated cell or tissue derived from a higher animal and kept in a solution of any kind is surrounded by this solution *on all sides*. Could we imagine the chemical processes within these cells held in abeyance, then we see how they would after a time succeed in getting into a state of equilibrium with their surroundings. When such an equilibrium has been established, the cells neither absorb nor secrete water. Only as this equilibrium is disturbed, either through changes in the surroundings of these cells or through the specific chemical changes occurring in the cells, can we expect a renewed absorption or secretion.

Under quite different conditions do we find the individual cells of the multicellular organism existing in the intact living body. While in a certain sense the internal activities of the ameba may be compared with those of the individual cells making up, say the intestinal mucosa, and while there exists a certain analogy between the two in the fact that both are surrounded by a liquid medium, here the analogy stops. *For while the ameba is surrounded on all sides by the same liquid medium, the cells of any of the absorptive or secretory organs, found for instance in a mammal, are through different portions of their cell protoplasm in contact with entirely different media.* The cells constituting the intestinal mucous membrane, for example, are bathed on one side by intestinal contents; on the other by blood or lymph, or both together. Such cells, like any other absorptive or secretory cells similarly situated, find themselves, therefore, in the predicament of trying to get into equilibrium with as many different media as surround them. It is in trying to do this that all the phenomena that we call absorption and secretion in the higher animals are produced.

It is in the attempt to get into equilibrium with the intestinal contents on the one side, and the blood on the other, that the

mucosal cell (better, the colloid membrane separating the intestinal contents from the blood), absorbs the intestinal contents and transfers them to the blood. How this is accomplished will now be discussed.

II

ON ABSORPTION

1. General Remarks on the Physico-chemical Structure of an Absorbing System in the Complex Organism

It follows as a necessary conclusion from our argument that *in the resting state the body of a multicellular living organism —a mammal, for example—is built up of a system of different hydrophilic colloids saturated with water. To be counted in with the structures that make up this water-saturated colloid system and composing an integral part thereof, are the blood and the lymph.* It may at first sight seem somewhat surprising that the blood and lymph are included, but the relation between the colloid and the water of fluid (hydrophilic) colloids, (sols), is identical with that of the relation between colloid and water in solid colloids (gels) such as fibrin. This identity is not only demanded by physico-chemical theory, but is proved experimentally by the work of Wolfgang Pauli and Hans Handovsky [1] on blood serum.[2]

That the entire mixture of solid and liquid colloid material constituting the organism is saturated with water is evidenced by the fact that we cannot make it, as a whole, take up any more water or give up any except as chemical changes are first produced in it which either increase or decrease the capacity of its colloids for holding water. In consequence, an organism not subject to any marked changes from without or within maintains a constant weight over long periods of time. We need but recall how all the secretions of a man undergoing absolute starvation drop to practically nothing, and how, on the other hand, the consumption of even enormous amounts of water by the normal individual does not lead to the development of

[1] Wolfgang Pauli and Hans Handovsky: Biochem. Zeitschr., **18**, 340 (1909).

[2] See page 145.

the slightest œdema. We are accustomed to say that the kidneys quickly rid the body of any excess of water. Just why this is done will be discussed shortly. The chemical changes capable of altering the hydration capacity of the body colloids may be of a character to affect the constitution of the entire mass that composes the body of a multicellular organism; or they may affect only smaller parts. In the former case we get either an absorption or a secretion of water by the organism as a whole; in the latter, only a limited or localized absorption or secretion of water by the parts involved. It is even possible for chemical changes to be going on in one part which lead to an absorption of water, while other changes are going on in another part which lead to a secretion of water. Thus, conditions are so arranged in the body under normal circumstances as to favor almost constantly the absorption of water from the gastro-intestinal tract, while at the same time they favor the secretion of the urine from the kidneys.

An absorption system consists in essence of three parts or phases:

(1) A material to be absorbed.

(2) A membrane which does the absorbing, and

(3) The blood or lymph into which the absorbed substance finally gets.

In the case of the gastro-intestinal tract these general terms are synonymous with

(1) The gastro-intestinal contents.

(2) The gastro-intestinal mucosa with its specific cells and all their supporting structures, and

(3) The blood and lymph.

Let us consider for a moment their physico-chemical properties.

(1) The gastro-intestinal contents from a chemical point of view represent a widely varying mixture. Expressed physico-chemically, however, they are a mixture of colloids and crystalloids in water. In the process of digestion the colloids are for the most part converted by a series of chemical cleavages into crystalloids. Thus, the proteins are broken into amino-acids, the fats into fatty acid and alcohol (glycerin), the carbohydrates, when digestible, into the simple hexose sugars. In the end, the absorption of the gastro-intestinal contents becomes

really, therefore, the problem of the absorption of a watery solution of various crystalloids.

(2) The membrane through which the intestinal contents are absorbed into the blood and lymph is made up of all the cellular and intercellular elements found between the gastro-intestinal contents on the one side and the circulating blood and lymph on the other. From a histological standpoint we know that this membrane is very different in different parts of the gastro-intestinal tube. With the different cells we must always in our considerations count in the intercellular substance that binds them together. From a physico-chemical standpoint this membrane is colloid in constitution. It is made up, in the main, of a mixture of various hydrophilic colloids. As a whole it is more or less solid in nature, like a leaf of gelatin soaked in water. But in no sense are the different portions of the gastro-intestinal tube made up of exactly the same colloid material, either in a chemical or a physical sense. We know this to be true because its different parts take up dyes, for example, with very different avidities when these are injected into the circulating blood.

We have now to point out that while the colloid membranes with which we busy ourselves in the laboratory are made up of *dead* material, that separating the gastro-intestinal contents from the blood and lymph is *alive*. This does not imply, however, that we must at once become vitalists. It only means that it introduces a series of more or less independent chemical and physico-chemical reactions into our general problem of absorption which demand additional care and study to analyze. The physico-chemical state of this living membrane is dependent upon the chemical changes that occur in the cells constituting this membrane, and these chemical changes are in turn intimately connected with the changes that occur in the blood supplying these cells. It is readily apparent, therefore, that the introduction of a single variable into the circulation may upset the entire chemistry of the cells of the absorbing membrane, and so their physico-chemical state. This is why what looks like such a small change in our entire absorption system may be followed by a most profound effect upon absorption.

(3) The blood represents a mixture of various formed elements with a liquid menstruum. The formed elements are colloid

bodies (nucleated and non-nucleated cells) which react toward changes in their environment (acid, alkalies, salts, non-electrolytes, etc.), in the very definite ways already described. The liquid portion of the blood (the plasma) is a liquid colloid mixture of various proteins. It behaves like a solution of gelatin, obeying laws identical with those governing the behavior of the more solid proteins which we have already discussed. Mixed with it are normally a number of different salts and varying amounts of different non-electrolytes.

Absorption from the *peritoneal cavity* presents a problem fairly identical with that from the lumen of the gut. We need in the above paragraphs but to make the absorbing membrane consist of the peritoneal cells with their supporting elements instead of the mucosal cells with theirs. The blood and lymph remain the same, and the material to be absorbed from the peritoneal cavity may have under experimental conditions any composition we choose to give it. As absorption from the peritoneal cavity represents a somewhat simpler problem than absorption from the gut we shall consider it first.

2. Absorption from the Peritoneal Cavity [1]

In view of the excellent running accounts of absorption that may be found by consulting R. Heidenhain,[2] Ernest H. Starling,[3] E. Waymouth Reid,[4] H. J. Hamburger,[5] E. Overton,[6] Otto Cohnheim,[7] or Rudolph Höber,[8] it is needless to attempt any detailed definition of the present status of our

[1] See Martin H. Fischer: Kolloidchem. Beihefte, **2**, 304 (1911).

[2] R. Heidenhain: Hermann's Handbuch der Physiologie, **5**, Leipzig (1883); Pflüger's Arch., **56**, 579 (1894).

[3] E. H. Starling: Schäfer's Text-Book of Physiology, **1**, 285, London and Edinburgh (1898); Oppenheimer's Handbuch der Biochemie, **3**, 206, Jena (1909).

[4] E. Waymouth Reid: Schäfer's Text-Book of Physiology, **1**, 261, London and Edinburgh (1898); Phil. Trans. Royal Soc., **192**, 231 (1900); Journal Physiol., **26**, 436 (1901).

[5] H. J. Hamburger: Osmotischer Druck und Ionenlehre, **2**, 95, Wiesbaden (1904).

[6] E. Overton: Nagel's Handbuch der Physiologie, **2**, 774, Braunschweig (1907).

[7] O. Cohnheim: Nagel's Handbuch der Physiologie, **2**,607, Braunschweig (1907).

[8] R. Höber: Koranyi-Richter, Physikalische Chemie und Medizin, **1**, 295, Leipzig (1907).

knowledge of absorption. This is shown in a masterly way by these authors. Depending upon whom we consult we find suggested, as the forces active in this matter, variations in hydrostatic pressure, filtration, or the two combined; diffusion and osmotic pressure, with modifications of both as determined by different media, different membranes and different solutions; imbibition; and when these physical forces are found wanting, then the "peculiar" forces of living matter are called upon for help. How unsatisfactory are all these explanations is clearly evidenced by the divergence of scientific opinion and the mutual criticism that finds expression in the individual writings of these authors, and this in spite of the fact that the experimental grounds upon which they base their opinions agree very well with each other.

My own experiments referred to below were extremely simple in character, made purposely so in order to eliminate the many and great errors that creep into these absorption experiments as soon as anesthetics, operations, animal boards and elaborate pieces of apparatus are employed. Had it not been for the use of these, one might have contented himself with mere interpretation of the experimental facts already found by previous authors. How some of these procedures affect absorption will be pointed out at the proper place.

I used healthy guinea pigs which were kept on a liberal diet of timothy hay, corn and oats, with water *ad libitum*. In order to permit comparison with each other, the animals in each set of experiments were taken from the same cage and treated exactly alike. No anesthetic being necessary, none was given. The various solutions and the water, after warming to 38° C., were injected into the peritoneal cavity by means of a hypodermic needle. The animals were held only during the few moments necessary for the injection, after which they were allowed to run about in their cages. At the end of a specified time they were killed by a blow on the head, immediately opened, and the unabsorbed liquid contained in the peritoneal cavity aspirated, by means of a pump, into small flasks. The amount of fluid recovered was then measured.

Let it be noted that what is discussed primarily in these pages is the absorption of *water* from the peritoneal cavity. *A priori* no one would be inclined to look upon the absorption

of any solution as representing a single process, and yet, in practice, this is done and has been done constantly. On all sides we see discussed the absorption of a solution *as such*. *The absorption of a solution represents the composite of the absorption of the solvent, and the absorption of every individual substance dissolved in that solvent.* Absorption of solvent and absorption of dissolved substance may mutually affect each other (see below), but this does not make them identical, nor does it make the absorption of the solution a single process. Excellent experimenters have gone so far as to look upon the distribution of a dissolved substance (such as a dye) in a tissue as evidence that the *solvent* in which that substance was originally dissolved was present there, or at least had passed that way. This is a most serious mistake.

§ 1

When any liquid is injected into the peritoneal cavity and we find that after a time it has been absorbed, we know from anatomical considerations that it must have passed into the lymph and the blood streams after having traversed the cells and intercellular substance which originally separated these two circulating fluids from the liquid that was injected. If we try to formulate the problem in terms of physical chemistry, then our purpose is to discover how the absorption of a solution that has any composition we may choose to give it, is accomplished by two colloid, circulating liquids (which, for the sake of brevity, we will regard as *sols*) that are separated from this solution by a solid colloid membrane (a *gel*). It is of interest for our further discussion first to call to mind which of these two liquid colloids plays the more important rôle in this absorption. As the peritoneal cavity is usually regarded as an immense lymph space, one might on *a priori* grounds be inclined to look upon the lymphatic circulation as that chiefly concerned in absorption from this cavity. And yet that the lymph plays a subordinate part and the blood circulation the chief rôle is indicated by E. H. Starling and Tubby's[1] finding that dyes appear in the urine after injection into the peritoneal cavity before the lymph coming from the thoracic duct shows any color; by the observ-

[1] Starling and Tubby: Journal of Physiol., **14**, 140 (1894). Starling: Schäfer's Text-Book of Physiology, **1**, 304, London and Edinburgh (1898).

ation of Orlow,[1] who noticed no increase in lymph flow after intraperitoneal injections of salt solution; and by that of H. J. Hamburger[2] who found peritoneal absorption unimpaired after ligation of the thoracic duct.

But, after the point is established that absorption from the peritoneal cavity is brought about chiefly through the agency of the blood, we have yet to say *why* this is the case. It is evident that the answer to this question bears both a quantitative and a qualitative element. In the higher animals the lymph circulation stands quantitatively far behind the circulation of the blood. Other things being equal, the blood would therefore absorb more than the lymph in proportion as the blood flow through a part exceeds quantitatively the lymph circulation through the same part. But chemical differences between the two play, to my mind, an equally important part. The total colloid content of the blood is higher than that of the lymph.[3] But, beyond this, the blood suffers rapid temporary changes in chemical composition that the lymph does not. Chief among these are the quantitative variations in the content of oxygen and (especially) of carbonic acid as induced through respiration. Further changes in the composition of the blood are wrought through the diffusion of metabolic products into and out of it, as when the blood passes through the kidneys, active muscles, the liver, etc. While somewhat similar changes are induced in the lymph when this passes through various organs, the rapid variations that we find in the blood are for obvious reasons lacking. But these more marked and rapid changes in the blood, combined with its more rapid circulation, mean at the same time more marked and rapid changes in the surroundings of the various tissue cells about which this circulating medium passes. The equilibrium with their surroundings which these cells endeavor to establish is therefore continually being disturbed because of these changes in their surroundings; and, so long as this happens, so long must the cells absorb. And hence the greater

[1] Orlow: Pflüger's Arch., **59**, 170 (1895).

[2] H. J. Hamburger: Arch. f. (Anat. u.) Physiol., 281 (1895).

[3] Almost one-fourth of the blood is protein. Blood plasma contains to each 100 parts almost 9 parts of protein. Lymph contains 3.4 to 4.1 parts of protein. See C. Schmidt: Vierordt's Daten und Tabellen, 97, Jena (1888); J. Munk and Rosenstein: Arch. f. Physiol., 376 (1890).

importance of the blood circulation over the lymph circulation in this problem of absorption in the higher animals.

§ 2

Let us now turn to the problem of the *absorption of water* from the peritoneal cavity. When water is injected at body temperature into the peritoneal cavity of guinea pigs it is rapidly absorbed, as the following table shows:

TABLE LXXXVII

Guinea pig.	Weight in grams.	Amount of water injected in cc.	Amount of fluid in cc. recovered after one hour.
a	413	20.8	5.4
b	535	20.8	5.4
c	544	20.8	4.8
d	460	20.8	4.9

There is nothing new about this observation. Where we encounter difficulty is in saying *why* the water is absorbed. Against the generally accepted belief that water is under such circumstances absorbed because the osmotic pressure in the cells lining the peritoneum is higher than that of the distilled water, serious objections can be raised. We know that the peritoneum does not retain this water, but gives it up to the blood (chiefly). On the osmotic basis this secretion into the blood could therefore occur only because the blood has a higher osmotic concentration than the cell contents. As a matter of fact we know that body cells, lymph and blood have, to all intents and purposes, the same osmotic concentration. The still more serious objection that this osmotic conception of water absorption ignores entirely the important part played by the intercellular substances need not be discussed here. That an injection of water into the peritoneum makes the cells here take up water because of an increased hydrostatic pressure directly induced by the injection, or aided by the contractions of the abdominal muscles, etc., is also scarcely tenable. The injection, first of all, does not appreciably increase the intra-abdominal pressure; and secondly, absorption occurs when the abdomen is opened, or in a dead animal (see below).

We have no difficulty in interpreting the absorption of water from the peritoneal cavity as a colloid phenomenon. In order that the absorption of water may occur, the hydrophilic colloids of the peritoneum must only be unsaturated with water. But when we consider the fact that after a few cubic centimeters of water have been absobred from the peritoneal cavity, more may be absorbed if the injection is repeated and this almost without limit, then we have to conclude that *under normal circumstances the tissues composing the peritoneum are constantly unsaturated with water.* What we really have to discuss, therefore, are the conditions that combine to keep the colloids of these tissues unsaturated with water in the living animal.

The first of these is the continuous production of acid (carbonic acid) in the tissues composing the peritoneum. In consequence of this the capacity of the tissues for holding water is increased, and they absorb it from any available source. If water is present in the peritoneal cavity they will take it up. But this would only lead to a swelling of the peritoneal tissues. As in this process an upper limit would soon be reached and absorption cease, this alone cannot lead to the continuous absorption which is observed. A second variable must exist, and this is found in the circulation of the blood and the lymph. Through these the carbonic acid produced in the cells is constantly carried away. But to carry this away from the tissues is to reduce the capacity of the colloids of the peritoneum for holding water, which, in consequence, they now give up. *As long as the circulation is maintained in a normal way absorption from the peritoneal cavity must therefore be continuous, for while the tissues of the peritoneum are on the one side busy in absorbing water they are, on the other, busy in giving it up to the blood* along with their carbonic acid.

The blood also carries all water contained in it in combination with the colloids found in the blood. As the arterial blood, low in carbonic acid, (representing, as we have said, a liquid colloid solution saturated with water), enters the capillaries, there diffuses into it the carbonic acid that is being produced in the cells. Through this the capacity of the blood colloids to hold water is raised, they find themselves in an unsaturated condition, and so are able to absorb water from any available source. This could be water directly, though in the living body

it means that the blood robs any tissue of its water that is holding it with less avidity than that represented by the colloids of the blood. In the case under discussion the blood absorbs water from the tissues composing the peritoneum. The peritoneum, in its turn, takes water from the peritoneal cavity, if any is present there. The now venous blood, with its higher water-content, passes to the lungs, where its carbonic acid escapes. When this happens the blood colloids are unable to retain longer the water absorbed previously, and this becomes "free" in the blood. It is this "free" water that under normal conditions the kidney extracts from the blood, and, by a process the reverse of that which we have described for peritoneal absorption, secretes as urine.[1] To this question we return below.

§ 3

We can immediately apply an experimental test to this process of reasoning. If the blood coursing through the peritoneal tissues and the tissues themselves take up water only because their colloids are unsaturated with it, then clearly they should be unable to take it up when offered to them in their own form. In other words, they should be unable to absorb water from any "solution" in which all the water is held in combination with colloids in the same way as they hold it. As a matter of fact, they cannot, as proved by the following experiments with egg albumin, which represents a liquid in which all the water is bound to colloid material.

TABLE LXXXVIII

Guinea pig.	Weight in grams.	Amount and character of solution injected.	Amount of fluid in cc. recovered after one hour.
a	533	20.8 cc. water	5.4
b	537	20.8 cc. white of egg (natural)	18.4
c	555	31.2 cc. water	7.6
d	563	31.2 cc. white of egg (natural)	27.7

Similar experiments with blood are described later.[2] It is because the water is thus united to colloid material that blood and lymph remain so long in the peritoneal cavity; in fact they

[1] See section on Secretion, p. 325.

[2] See page 740.

cannot be absorbed from here or from the intestinal tract until ferments or other conditions have first so affected the colloids that they yield up their water in a " free " form.

§ 4

The effect on water absorption when the same amount of differently concentrated sodium chlorid solutions are injected intraperitoneally instead of plain water is indicated in Table LXXXIX.

TABLE LXXXIX

Guinea pig.	Weight in grams.	Amount and character of solution injected.	Amount of fluid in cc. recovered after one hour.
a	417	20.8 cc. water (control)	5.4
b	397	20.8 cc. m/12 NaCl	11.8
c	419	20.8 cc. m/8 NaCl	13.0
d	488	20.8 cc. m/6 NaCl	14.6
e	445	20.8 cc. m/4 NaCl	19.9

The interpretation of these findings is about as follows:

When, in place of pure water, a sodium chlorid solution is introduced intraperitoneally we may assume that the water of this solution tries to diffuse into the cells just as though the salt were not there. But, at the same time that this is occurring, the salt is also diffusing into the peritoneum. Just why this happens is discussed below. But the presence of the salt in the colloids of the peritoneal tissues will make these tend to give up water. The salts will, therefore, tend to counteract the effect of the carbonic acid in the cells. The normal fall which tends to make the water move from the peritoneal side of the peritoneal absorbing membrane to the vascular side will now be counteracted by one occurring in the opposite direction. The normal streaming of water which tends to make for an absorption from the peritoneum will be met by a counterstream which tends to make for a secretion from this structure. The end result, so far as absorption of water is concerned, will represent the algebraic sum of the two. If this second stream is not a great one, there will be only a slight reduction in the rapidity with which the water is absorbed. This is what happens with the dilute salt solution. But, as the concentration of the salt

increases, this counter-current must become more and more manifest, so that, as in the last experiment (*e*) of Table LXXXIX, practically no absorption (of water) occurs within the time limits set for the experiment.

§ 5

In equimolar concentrations different salts affect to very unequal degrees the absorption of water by colloids swelling in the presence of an acid. So also, and in the same general order, do they affect the absorption of water by the peritoneum.

TABLE XC

Guinea pig.	Weight in grams.	Amount and character of solution injected.	Amount of fluid in cc. recovered after one hour.
a	643	20.8 cc. m/8 sodium chlorid	7.0
b	594	20.8 cc. m/8 sodium acetate	10.0
c	551	20.8 cc. m/8 sodium nitrate	12.6
d	409	20.8 cc. m/8 sodium sulphate	20.0
e	496	20.8 cc. m/8 sodium citrate	23.4
f	492	20.8 cc. m/8 disodium phosphate	25.6

TABLE XCI

Guinea pig.	Weight in grams.	Amount and character of solution injected	Amount of fluid in cc. recovered after one hour.
a	343	20.8 cc. m/8 potassium iodid	3.4
b	335	20.8 cc. m/8 potassium bromid	8.8
c	322	20.8 cc. m/8 potassium chlorid	11.0
d	290	20.8 cc. m/8 potassium sulphocyanate	13.4
e	355	20.8 cc. m/8 potassium nitrate	13.4
f	354	20.8 cc. m/8 potassium acetate	16.8
g	363	20.8 cc. m/8 potassium tartrate (died 40 minutes after injection)	18.9
h	386	20.8 cc. m/8 potassium citrate (died 15 minutes after injection)	20.5

TABLE XCII

Guinea pig.	Weight in grams.	Amount and character of solution injected.	Amount of fluid in cc. recovered after one hour.
a	452	20.8 cc. m/8 potassium chlorid	12.8
b	396	20.8 cc. m/8 ammonium chlorid	13.7
c	484	20.8 cc. m/8 magnesium chlorid	19.4
d	476	20.8 cc. m/8 calcium chlorid	24.2
e	502	20.8 cc. m/8 strontium chlorid	24.4

As Tables XC, XCI, and XCII, show clearly, every one of the salts employed markedly retards the absorption of water from the peritoneal cavity. This harmonizes entirely with the fact that the presence of every salt inhibits the absorption of water by such a hydrophilic colloid as fibrin, gelatin or serum albumin which is swelling in the presence of an acid. But the parallelism between the two processes is even closer than this. We note in Table XC, for example, where the effects of equimolar solutions of sodium salts are compared, that the sulphate, citrate and phosphate have an effect far above that of the chlorid, acetate or nitrate in preventing absorption. In Table XCI, where the effects of a series of potassium salts are compared, the order of the acid radicals is again the familiar one observed in studies on pure protein colloids. Table XCII brings out the same fact for a series of different basic radicals. That the results should be so nearly identical with the effects of various salts on pure colloids is really somewhat surprising when we remember that in such experiments as these one is compelled to work with a considerable experimental error, arising from the fact that in each of these series several animals are used, that we cannot control the amount of water consumed by them just before being used, that we cannot escape the specific poisonous effects exerted by the different salts employed, etc. Nevertheless the experimental results are point for point almost identical with the findings on pure colloids. This indicates to my mind how predominant is the colloid element in this problem of absorption.

§ 6

As compared with the effect of electrolytes, various non-electrolytes affect the absorption of water by colloids in the presence of any acid only slightly. Table XCIII gives the results obtained when solutions of various non-electrolytes in concentrations osmotically about equivalent to the solutions of the various salts used above, are injected intraperitoneally:

It is clear from this table that ethyl and methyl alcohols do not delay the absorption of water from the peritoneal cavity. On the other hand, glycerin and the two sugars used produce a decided inhibition. The sugars even produce a secretion of

fluid. The effects again agree with the findings on pure colloids where only the last-named produce in the higher concentrations a dehydration.

TABLE XCIII

Guinea pig.	Weight in grams	Amount and character of solution injected.	Amount of fluid in cc. recovered after one hour.
a	425	20.8 cc. m/4 ethyl alcohol	5.8
b	434	20.8 cc. m/4 methyl alcohol	2.1
c	464	20.8 cc. water (control)	5.6
d	583	20.8 cc. m/4 urea	11.7
e	569	20.8 cc. m/4 glycerin	18.2
f	687	20.8 cc. m/4 glycerin	17.4
g	521	20.8 cc. m/4 cane sugar	25.7
h	725	20.8 cc. m/4 cane sugar	27.0
i	522	20.8 cc. m/4 dextrose	26.3
j	710	20.8 cc. m/4 dextrose	29.0

§ 7

Both alkalies and acids when injected intraperitoneally delay the absorption of water, as indicated in the following table:

TABLE XCIV

Guinea pig.	Weight in grams.	Amount and character of solution injected.	Amount of fluid in cc. recovered after one hour.
a	544	20.8 cc. water (control)	4.7
b	545	20.8 cc. n/100 NaOH	6.2
c	543	20.8 cc. n/50 NaOH	11.0
d	568	20.8 cc. n/25 NaOH	10.6
e	460	20.8 cc. water (control)	4.8
f	460	20.8 cc. n/100 HCl	7.4
g	447	20.8 cc. n/50 HCl	12.4
h	450	20.8 cc. n/33 HCl	12.0

In explanation of these results the following is offered. In the concentrations employed both acids and alkalies produce an excessive swelling of the peritoneal tissues. This excessive swelling *delays* absorption, not alone by occluding the lumina of the capillaries supplying the peritoneum and so decreasing the absolute blood flow through these tissues, but by so increasing the avidity of the peritoneal tissues for water that the blood passing through them is not enabled to take the water away from them with its usual ease.

§ 8

Table XCV shows how water and various salt solutions are absorbed from the peritoneal cavities of *dead* animals. The guinea pigs were killed by a blow on the head, and injected subsequently in the same way as in the experiments with living animals. After injection, the animals were turned about a few times to allow the liquids to spread through the peritoneal cavity, and were then laid quietly on their bellies for one-half hour, after which they were turned on their backs for one-half hour.

TABLE XCV

Guinea pig.	Hours dead.	Weight in grams.	Amount and character of solution injected.	Amount of fluid recovered in cc. after 1 hour.	Recovered from second pouring in of 20.8 cc. water after 1 hour.
a	just dead	331	20.8 cc. water	7.6	
b	just dead	396	20.8 cc. water	9.0	
c	1.00	333	20.8 cc. water	9.4	15.3
d	2.30	351	20.8 cc. water	9.3	15.0
e	7.30	395	20.8 cc. water	8.0	
f	24.00	375	20.8 cc. water	12.5	
g	48.00	353	20.8 cc. water	17.0	
h	0.15	267	20.8 cc. m/8 NaCl	13.2	
i	0.15	295	20.8 cc. m/8 Na_2SO_4	10.6 [1]	
j	0.15	299	20.8 cc. m/8 sodium citrate	11.4 [1]	

[1] A part of the peritoneal fluid was accidentally lost.

The table shows that water is readily absorbed from the peritoneal cavities of dead animals. How is the result to be explained? The answer is not essentially different from that given for the living animal. An acid production in the tissues is again responsible for increasing the capacity of the tissue colloids for holding water. Only, while we attributed this to carbonic acid in the living animal, we can attribute it in the dead animal not only to this acid, but in addition to lactic and the other acids that we know are produced postmortem. The longer an animal is dead, the higher we may assume becomes the concentration of the acids in the various tissues. On this basis we might expect a progressively greater absorption of water with every increase in the length of time that an animal is dead. But this could hold only within certain limits, for in pure colloids we know that with a progressive increase in acid concentration

the absorption of water increases only up to a certain point, after which a decreased absorption is noted. The same is evident in Table XCV, where animals long dead (*f* and *g*), show a decidedly lower absorption of water than animals dead only a short time.

As is sufficiently well indicated by the results obtained with animals, *h*, *i* and *j*, various salts retard the absorption of water from the peritoneal cavity of dead animals as they do in living animals, and, we would add, for the same reason.

3. Absorption from the Gastro-intestinal Tract

The foregoing paragraphs, which show that the same conditions that retard the absorption of water by such hydrophilic colloid as fibrin or gelatin, retard in almost identical fashion the absorption of water from the peritoneal cavity, prove, it seems to me, that the two processes are in essence the same. What is next in order is to compare this process of peritoneal absorption with the processes of absorption as observed in other regions of the mammalian organism to see if the conclusions drawn regarding absorption as observed in the peritoneal cavity cannot be extended to cover at least some of these. Of chief interest in this connection, because of its physiological importance, is *absorption from the intestinal tract.*

To anyone conversant with the wealth of experimental data on alimentary absorption that has been accumulated by Voit and Bauer,[1] R. Heidenhain,[2] Franz Hofmeister,[3] H. J. Hamburger,[4] R. Höber,[5] G. B. Wallace and A. R. Cushny,[6] Otto Cohnheim,[7] E. Waymouth Reid[8] and G. Kövesi,[9] the following are familiar facts:

[1] Voit and Bauer: Zeitschr. f. Biologie, **5**, 536 (1869).

[2] R. Heidenhain: Pflüger's Arch., **56**, 579 (1894); **62**, 331 (1896).

[3] Franz Hofmeister: Arch. f. exp. Path. u. Pharm., **28**, 210 (1891).

[4] H. J. Hamburger: Osmotischer Druck und Ionenlehre, **2**, 168, Wiesbaden (1904), where references to his earlier papers will be found.

[5] Rudolph Höber: Pflüger's Arch. from **70** on; see his many papers during the years 1898 to date.

[6] G. B. Wallace and A. R. Cushny: Am. Journal of Physiol., **1**, 411 (1898); Pflüger's Arch., **77**, 202 (1899).

[7] Otto Cohnheim: Zeitschr. f. Biol., **36**, 129 (1897); **37**, 443 (1899).

[8] E. Waymouth Reid: Journal of Physiol., **21**, 85 (1897); **22**, 56 (1898); **26**, 427 (1901).

[9] G. Kövesi: Centralbl. f. Physiol., **11**, 553 (1897).

When water is introduced into a segment of intestine it is rapidly absorbed. All salt solutions, *so far as the water in them is concerned*, are absorbed less rapidly than the pure water. The concentration of the salt solution is an important factor in this phenomenon. When sodium chlorid solutions of different concentrations are compared, they are found to be absorbed the more slowly the higher the concentration of the salt. If sufficiently strong solutions are employed there may first result a pouring out of liquid into the lumen of the gut, so that the solution becomes diluted, after which it is slowly absorbed.

When the absorption of equimolar (or better, osmotically equivalent) solutions of different salts is studied, it is found that these are absorbed at very different rates. The effect of any salt in a solution upon the absorption of water from that solution may be thus stated: With a given base, the acid radicals arrange themselves in the following order, where that which retards least is given first:

Chlorid, bromid, iodid, nitrate, sulphate, phosphate.

With a given acid, the order of the basic radicals is as follows (R. Höber), that least effective in preventing absorption being given first:

Potassium, sodium, calcium, magnesium, barium.

It is easy to see that the order of the various salts is practically identical with that found above in the experiments on peritoneal absorption. The position of the acetate, tartrate and citrate, not given in the above lists, can be determined by consulting the tables of Wallace and Cushny, when it is found that they occupy a place in the absorption of water from the gut which is the same as that occupied by them in the case of peritoneal absorption.

With any of these salts, as with ordinary sodium chlorid, the delay in the absorption of the water grows with the concentration of the salt. A point is finally reached where such water as is introduced into the intestine is not only not absorbed, but water is secreted into the gastro-intestinal tract. This concentration point lies high in the case of sodium chlorid, sodium bromid, etc., but very low in the case of sodium sul-

phate, phosphate, tartrate, citrate, etc. This is one of the chief reasons why the last named are known as " saline cathartics." Point for point, therefore, *the absorption and secretion of water by the gut is identical with the absorption and secretion of water by the peritoneum, and both are comparable to the absorption and secretion of water by simple protein colloids when placed in like surroundings.*

The identity of the processes of absorption from the peritoneal cavity and from the intestinal lumen goes even further. The rapid absorption of aqueous solutions of various alcohols from the intestinal tract shows that these non-electrolytes do not interfere with the absorption of water even when present in concentrations osmotically equivalent to those of the active salts. Sugar solutions and glycerin also behave in the intestinal tract, so far as the absorption of water from their solutions is concerned, as they do when introduced intraperitoneally. The slow absorption of water, or, in response to the introduction of a solution of sufficiently high concentration, the actual secretion of water into the gut, is evidenced not only by direct experiment, but by everyday clinical experience. Are not the sugars, when consumed in any considerable quantities, capable of producing watery stools (independently of any previous fermentation with the production of organic acids), and do not glycerin enemas produce the same secretion of water into the bowel that results when enemas containing any of the saline cathartics are employed?

We have interesting parallels also of the peritoneal experiments which showed that water when united to a hydrophilic colloid is incapable of being absorbed without first being freed. Thus, protein solutions (such as egg white, blood, or blood serum) are not absorbed from the intestinal tract unless proteolytic ferments are present which, by acting on the proteins chemically destroy their markedly (hydrophilic) colloid character, and so liberate the water held by them. In this way also can we understand the behavior of cellulose and, especially, agar-agar in preventing constipation. One of the commonest causes of constipation resides in the too perfect absorption of water from the gastro-intestinal contents. It is a time-honored custom to suggest the addition of vegetables to the diet of such individuals. In addition to the action of the salts (citrates, tartrates, etc.) obtained from vegetables and the effects of the production

(through fermentation) of certain organic acids in the bowel which alone tend to prevent a too great absorption of water from the gastro-intestinal contents, the high cellulose content of such a diet (that is to say, its high hydrophilic colloid content) makes it impossible for the mucosa to get the water out of it. Since cellulose is not changed (except very slightly by certain bacteria) in its passage through the gastro-intestinal tract, it retains all the water with which it was saturated before being consumed, or with which it saturates itself in its course through the alimentary tract. The same explanation holds for agar-agar or the feeding of any of the Japanese sea weeds from which this is prepared. Agar-agar is a hydrophilic colloid incapable of being affected chemically in its passage through the gastro-intestinal tract (L. B. Mendel and Saiki), and so any water that it may have absorbed before being swallowed, or may absorb in the gastro-intestinal tract, is retained. In this way the inspissation of the gastro-intestinal contents (and so the constipation) is prevented.

These paragraphs suffice to show that the colloid-chemical theory is adequate to explain the *qualitative* aspects of water absorption in the complex organism. It remains to show that it is also adequate from a *quantitative* point of view. This is easily done. *The anatomical and physiological conditions existing normally in the body tend to keep the colloids of the gastro-intestinal tract and of the blood and lymph streams passing through it in an unsaturated condition so far as water is concerned, while the reverse conditions hold for any secreting organ such as the kidney.*

The mouth and esophagus play practically no rôle in the absorption of water. The stomach, according to von Mering's experiments, also takes but little if any part in the absorption of water. The small and large intestine are the absorptive organs for this substance *par excellence*. The stomach is richly supplied with arterial blood. The small and large intestine are also generously supplied, but not as generously as the stomach. The separate branches of the mesenteric arteries which go to supply the villi occupy a fairly central position in this structure and break up into a capillary network which lies close under the intestinal epithelium. As clearly evidenced by the dark color of the portal blood, and direct gas analysis, the blood returning from the intestine is intensely venous (poor in oxygen and rich in car-

bonic acid). The experiments of VON LIMBECK, GÜRBER, and HAMBURGER [1] show that under the influence of such an increase in carbonic acid concentration as exists *normally* in venous blood over arterial blood the red and white corpuscles absorb an amount of water which easily amounts to from 5 to over 15 per cent [2] of their volume in arterial blood. If we use only the lower of these values and ignore entirely the water-carrying power of the colloids contained in the plasma, a little calculation shows that every liter of blood passing through the intestinal tract is capable of absorbing 17.5 cc. of water, for the corpuscles when moist make up, in round numbers, about 35 per cent of the blood. Even these values, which have been chosen as *low* as possible, easily suffice to account for the absorption of great amounts of water from the gastro-intestinal tract.

4. Historical and Critical Remarks on the Theory of Absorption. Peritoneal and Alimentary Absorption of Dissolved Substances.

Let us now consider for a moment the explanations of absorption that have been given by other authors, and select from them not only the elements which we ourselves think to be correct, but point out, with the help of a few examples, how certain experiments which have long stood as the bulwark of "physiological" or "vitalistic" interpretations of certain life phenomena are easily explained on the colloid basis, and how others long held to support different theories of absorption fall in with the colloid one.

[1] H. J. HAMBURGER: Osmotischer Druck u. Ionenlehre, **1**, 291, Wiesbaden, (1902); ibid., **1**, 404 (1902).

[2] These figures are nearly doubled if instead of comparing the sizes of the corpuscles in arterial and in *ordinary* venous blood the sizes in arterial and *passively congested* venous blood are compared. In other words, the same circumstances that make the passively congested *organ* become œdematous make the corpuscles *in the blood* become "œdematous," and since the (colloid) plasma also "swells," venous blood or "passively congested" blood is, if water is available, richer in water than normal arterial blood. The blood is "hydremic," but this hydremia is not the cause of an œdema; it is an œdema itself, and an expression of the same factors which make the more solid tissues "œdematous."

§ 1

For half a century various authors have thought that *filtration* plays an important part in the absorption of liquids. According to definition, filtration represents the passage of a liquid through a separating membrane of some sort in consequence of differences in hydrostatic pressure. On this basis it has been held that a liquid is forced from the lumen of the gut or from the peritoneal cavity into the blood because of a pressure within the gut or peritoneal cavity (produced through gas or the action of muscles of various kinds) which exceeds the pressure in the blood. Such a belief has been supported by the experiments of LEUBUSCHER and H. J. HAMBURGER,[1] who found that with an increase in intra-intestinal or intra-abdominal pressure there resulted an increase in absorption, at least up to a certain point. Without for the moment questioning the correctness of the experimental finding itself (a serious error enters into it) we know that such an intra-intestinal or intra-abdominal pressure is not necessary for absorption. E. WAYMOUTH REID [2] found absorption (of water) to occur from the intestine of the dog, when the pressure within the gut was decidedly lower than that in the mesenteric veins, and HAMBURGER himself describes experiments in which he observed a ready absorption of water from the peritoneal cavity when the abdomen was opened or when the animal was dead.

After what has been said above regarding water absorption as a colloid phenomenon these findings are entirely to be expected. What is needed is an interpretation of LEUBUSCHER and HAMBURGER'S experiments with changes in pressure. LEUBUSCHER'S result has been explained by saying that through increased intra-intestinal pressure the folds of the intestinal mucosa are smoothed out, and so an increased surface of gut is rendered available for absorption. But this explanation has not been accepted as complete by HAMBURGER, who found an increased absorption from the gut with every increase in pressure up to a certain point, even after surrounding the intestine with a wire cage which prevented its unfolding. In explanation of HAMBURGER'S result, I would agree with the view that with the first increase

[1] H. J. HAMBURGER: Osmotischer Druck und Ionenlehre, **2**, 176, Wiesbaden (1904).

[2] E. WAYMOUTH REID: Phil. Trans. Royal Soc., **192**, 231 (1900).

in pressure the flow of blood out of the veins is favored. In consequence of this the blood flow through the gut is favored and so the conditions for absorption. With a further increase in pressure, the blood vessels are compressed, and now the blood flow is diminished, in consequence of which a decrease is absorption is observed, as HAMBURGER found.

Consideration of the available experimental facts must therefore make one largely unwilling to look upon filtration as a factor of any large importance for the passage of liquid from the peritoneal cavity or the lumen of the gastro-intestinal tract into the blood. But while the absorption of water may occur without the existence of pressure differences this does not say, of course, that such pressure differences when they do arise under certain circumstances may not then be of *some* physiological importance. But to my mind, this can never be great. The final answer to the problem, however, depends upon what is the structure (the porosity) of the colloid membranes through which the water is supposed to be forced and the differences in pressure available in the body for a filtration. To the discussion of these points we return later.[1]

§ 2

The question of *osmotic pressure* (even as modified through the conception that the surface layer of the cells is lipoid in character) in the problem of water absorption from the peritoneal cavity or the gut needs no special discussion—its inadequacy to explain the phenomena of absorption as observed here is admitted on all sides. That it is still adhered to, no doubt depends on the fact that we have had nothing more adequate to substitute for it; and any number of biological workers have been unwilling to believe that a present inability to explain on a purely physico-chemical basis all the phenomena of absorption (or secretion) presages that such will never be forthcoming, and that, in consequence, support is lent "physiological" or "vitalistic" conceptions of the process. It seems to me that on the basis of what has been said in these pages and in my previous papers, we are now in a position where we not only may, but must, discard the osmotic conception of cell behavior so far as water

[1] See pages 371 and 380.

absorption is concerned. We must also discard it so far as *the absorption of dissolved substances* is concerned.

As already noted, if cells were surrounded by semi-permeable films, as demanded by the osmotic theory, dissolved substances could neither get into nor out of them. Yet both must be possible, as well as the movement of water into and out of cells, otherwise their life would cease. Dissolved susbtances get into and out of cells by diffusion. The rôle of this factor has been recognized and discussed as active in the process of absorption since the days of Carl Ludwig. R. Heidenhain succeeded in minimizing its importance in the analysis of the whole problem by showing that an absorbed fluid (or a secretion) usually differs in quantitative composition from the source from which it was derived. On this is based his belief in the selective " physiological " character of absorption (and secretion). There is nothing surprising about these phenomena to us. We expect them, in fact. As has been said, *a solution is never absorbed (or secreted) as such.* Whenever a solution is seen to be absorbed (or secreted), we are observing the composite of the absorption (or the secretion) of the solvent plus the absorption (or secretion) of each individual substance dissolved in that solvent. When any solution is introduced into the intestine, for example, each one of the dissolved substances diffuses into the wall of the intestine until an equilibrium is established in the distribution of each of these substances between the (liquid) phase represented by the solution and the more solid phase represented by the (colloid) intestinal wall. Similarly, every substance present in the intestinal wall tends to diffuse out into the solution to the establishment of an equilibrium.

In biological material it has been very generally assumed that the distribution of dissolved substances between two such phases should attain equilibrium when the concentration of any dissolved substance is the same in both. Such an *a priori* conclusion is entirely unjustified. We deal in this problem with the distribution of a dissolved substance between water and a colloid, and, as we know from the facts now available on this subject, equilibrium may be reached when the dissolved substance is contained in less, the same, or a higher concentration in the colloid than in the solution surrounding it.[1]

[1] Franz Hofmeister: Arch. f. exp. Path. u. Pharm., **27**, 395 (1890); **28**, 210 (1891).

Now, while the absorptive membrane is trying to get into equilibrium with the solution to be absorbed on the one side, it is also trying to get into equilibrium with the blood on the other. The whole absorptive system consists of the three phases (the material to be absorbed, the colloid absorbing membrane, the liquid colloid blood and lymph) already discussed, and *the problem of the "selective" absorption of the dissolved substance is the problem of the agencies concerned in establishing an equilibrium between all the various dissolved substances in these three phases.* The factors of greatest importance in such a problem are the character of the various colloids concerned, and their physico-chemical state as determined through the presence of acids, alkalies, salts and various non-electrolytes; the nature of the dissolved substance to be absorbed, as its rate of diffusion; the presence or absence of lipoids in the colloid, absorbing membrane and in the blood, etc. In other words. the laws of adsorption, of partition, and of chemical combination are all at work. To the process of simple diffusion in this matter of absorption (or secretion) become added therefore a series of secondary phenomena that obscure its purity.

To illustrate what has been said, let us try to follow the relatively simple process of the absorption of a strong (so-called hypertonic) sodium chlorid solution when this is introduced into the peritoneal cavity, or into the intestine. Both the water and the salt begin immediately to diffuse into the absorbing membrane. As this progresses, the concentration of the sodium chlorid in the absorbing membrane rises. This rise in concentration so affects the colloids of the absorbing membrane that they stop taking up water, or, if sufficiently strong, an actual secretion of water into the peritoneal cavity or the gut may follow. While this is occurring, an equilibrium is tending to be established between the concentration of the sodium chlorid in the solution undergoing absorption and the sodium chlorid in the absorbing membrane. But this is never attained under normal circumstances, because the salt in the absorbing membrane is at the same time trying to get into equilibrium with the sodium chlorid in the blood. Now, since this is circulating, it is evident that the equilibrium is constantly being broken down toward the side of the blood. In consequence of this, more and more salt must move over into the blood (be absorbed). But, as this occurs, the state of the colloids of the

absorbing membrane again returns to a more "normal" one and so the absorption of water, which could not occur before, can again take place.

With a dilute (a hypotonic) solution of sodium chlorid the water does not meet with so great a resistance to absorption, and it is, therefore, possible for the dilute salt solution to become more and more concentrated as the water is (the more rapidly of the two) absorbed from it.

Even salt solutions isotonic or isosmotic with the blood must be absorbed. Though such a solution cannot be absorbed on the osmotic basis because no differences in osmotic pressure exist to make the water move, there is no difficulty in interpreting what happens on the colloid basis. Let the colloids of the absorbing membrane take a little water from the isotonic solution and salt must quickly follow, for now its concentration is no longer in equilibrium with that of the sodium chlorid in the absorbing colloid membrane. Then more water goes in, and then more salt, until all is absorbed. Or we could start the absorption by having a little salt go in first and then the water, etc., for if the truth be told we do not yet know just what concentration characterizes the "isotonic" solution, nor shall we until the colloid constitution of living matter has been adequately taken into account.

Finally, on the basis of these conceptions of absorption, we experience no difficulty in understanding why any solution remaining for longer periods in the peritoneal cavity or in the intestine (while being "absorbed") has substances found in the blood or tissues appear in it which it did not originally contain. As dissolved substances diffuse out of a solution undergoing absorption into the absorbing membrane until an equilibrium is established, just so, of course, must the substances contained in the absorbing membrane tend to diffuse into the solution. It has been generally held that this diffusion of salts (and other substances) out of an absorbing membrane into a solution that is being absorbed constitutes "an attempt to establish osmotic equilibrium between the two." As a matter of fact such a conclusion is premature if nothing more. We do not yet know all the factors involved in determining the point of equilibrium in the body, in the distribution of the various dissolved substances between the phases concerned. One thing,

however, is certain and that is that the final equilibrium is not a simple osmotic equilibrium. This is clearly enough evidenced not alone by the well-known fact that the physiological behavior of different salts, in this process of absorption, for example, bears no relation to their osmotic concentration, but by the further fact that the distribution of most dissolved substances between a colloid and a solvent is practically never the same in both. *The "selective" character of absorption depends upon the fact that the absorption of water in the living organism is a process entirely separate from the absorption of dissolved substances. Of the latter each moves at its own rate, and is influenced in its movement by factors that may not affect others in the same way or to the same degree. A dissolved substance may actually be absorbed while water is being secreted, and vice versa.* Thus, to produce catharsis a saline cathartic diffuses into the wall of the gut (is absorbed) while water is being given off (is being secreted); and salts diffuse into the distilled water introduced into the bowel while this is being taken up by the mucous membrane. Such facts would be impossible of explanation if the cells had "osmotic," "lipoid," or similarly constituted "membranes" about them. If what is here written will be kept in mind the "selective" character of absorption ceases to produce astonishment—it would be more strange were it not selective.

§ 3

The workers in physiology and experimental medicine, who have called attention to the *"secretory" and "physiological" activities* of absorbing (and secreting) membranes and to the "physiological driving force"[1] situated in them, are deserving of blame or praise depending upon whether they used these words in the despairing attitude of those biological workers who believe that life phenomena will never be interpretable solely in the terms of the physical sciences, or as convenient heads under which to group certain of the phenomena of absorption and secretion which could not be so analyzed at the time they prosecuted their scientific studies. But the necessity of retaining these terms, even in the latter sense, may now largely

[1] "Physiologische Triebkraft" of the Germans.

disappear. The "secretory" activities of absorbing (and secreting) membranes as evidenced through their "selective" absorption and secretion of water and dissolved substances we have already discussed in the preceding paragraphs. Their "physiological" activity retains a meaning only in the sense that the absorbing (and secreting) membranes of multicellular organisms contain living cells in each of which there are occurring well-ordered series of chemical and physico-chemical reactions which are capable of influencing the colloid constitution of these membranes. To do this is to influence the nature of the phases and the conditions of equilibrium in our absorptive (secretory) systems, and therefore secretion and absorption. But these reactions are not impossible to analyze.

The need for the "physiological driving force" also disappears. Such was originally called upon to help explain such a fact as the absorption of a solution, from the intestine for example, when the pressure under which it stands in the lumen of the gut is less than that of the pressure of the blood in the mesenteric veins through which it is being absorbed (E. Waymouth Reid). Such a view regards absorption as a process in which water is *forced* into the tissues. This is not what happens. It is *sucked* in, and such a process can occur even when the hydrostatic pressure in the veins happens to be a few millimeters above that in the lumen of the intestine. The pressures produced in the swelling of hydrophilic colloids are enormous as compared with the highest hydrostatic (arterial blood) pressures ever observed in animals possessed of a circulation. The use of "physiological" poisons to illuminate the "physiological" element in absorption (or secretion) proves nothing. Such poisons simply constitute a direct or indirect means of altering the physico-chemical state of the absorbing (or secreting) structures. And is it not the problem of physiology to state in terms of physics and chemistry just what this "normal" absorption (and secretion) is? When we use a "physiological" poison we have to explain the action of the poison along with what constitutes "normal" absorption (and secretion).

Nothing has perhaps so effectively hampered the acceptance of the belief that absorption (and secretion) would ultimately prove themselves completely analyzable physico-chemically, and fostered the continuation of the "physiological," "secretory,"

etc., notions of absorption (and secretion) as a series of experiments first described by R. Heidenhain, and more recently repeated in modified form by E. Waymouth Reid and Otto Cohnheim. The most striking of these is the often quoted experimental finding that a dog will absorb his own blood serum. A word regarding experiments of this character may serve to show how they are interpretable on the basis of the colloid theory of water secretion and absorption. *In not one of these experiments, except where the possibility of the presence of proteolytic ferments is not excluded, is the serum or plasma completely absorbed.* The reason why some is absorbed, but never all, is clear from the following:

Blood serum and blood plasma are not blood; they are blood minus much of its hydrophilic colloid content. They are not solutions in which all the water is bound to colloid material as in normal blood, but they contain "free" water over and above that necessary to saturate the colloids remaining in the "serum" or the "plasma." When they are introduced into the intestine they are therefore absorbable but only in so far as they contain free water (and a certain proportion of salts, urea, etc.) The absorption comes to a halt as soon as water has been absorbed down to the point where the remaining water is combined with colloid. In these experiments things are therefore *not* the same on both sides of the absorbing membrane. The animal does not absorb serum or plasma as such, much less what these authors seem at times to try to have us believe, namely, something identical with blood itself. The animal absorbs some water and a few dissolved substances, and it does this for the same reason that it absorbs under similar circumstances any ordinary "physiological" salt solution.

§ 4

Of the different factors that are cataloged in our treatises on physiology, and which have at various times and in various ways been looked upon as active in this problem of absorption, only one remains to be discussed—that of *imbibition.* What Adolph Fick[1] has called molecular imbibition is but another

[1] Adolph Fick: Medizinische Physik, 3d Ed., Braunschweig (1885).

term for what we to-day call the absorption of water by hydrophilic colloids. It is, therefore, of interest that mention is made of imbibition as being important in the general problem of absorption as far back as 1881.[1] But the real significance of imbibition as a factor concerned in absorption was only pointed out more recently by H. J. HAMBURGER.[2] This author correctly emphasized the theoretical importance of his observation that animals absorb various solutions from their peritoneal (and other serous) cavities after death. While we cannot agree with the details of his ideas outlining the way in which the forces of imbibition act normally, a discussion into which it is not necessary to go here, there is no disputing his claim that imbibition plays a rôle. But HAMBURGER does not regard imbibition as the most significant factor in absorption, and continues to hold to the ideas of filtration, osmotic pressure and the " mitschleppende Wirkung " of the circulation as also concerned in the process. Nor does he suggest any way by which a fluid absorbed by imbibition is again gotten rid of. In view of all this, it seems to me that we owe a special debt to FRANZ HOFMEISTER,[3] who, as early as 1891, pointed out that the salts which make (partially) water-soaked gelatin discs give off their water (secrete it) are identical with the so-called saline cathartics, and suggested that the two processes are in essence the same. In spite of the numerous papers on alimentary absorption and secretion, and on the mode of action of the saline cathartics that have appeared since HOFMEISTER'S writings, there seems little question that we are destined to return to HOFMEISTER'S conclusions, and find in them not only an explanation of the mode of action of these cathartic salts, but a model of that which constitutes the essence of absorption and secretion.

[1] W. VON WITTICH: Hermann's Handbuch d. Physiol., **5**, 2ter Theil, Leipzig (1881).

[2] H. J. HAMBURGER: Osmotischer Druck und Ionenlehre, **2**, 108 and 164, Wiesbaden (1904).

[3] FRANZ HOFMEISTER: Arch. f. exp. Path. u. Pharm., **28**, 210 (1891).

III

ON SECRETION

1. Introduction

The paragraphs on absorption have shown how water and various dissolved substances get from the lumen of the gut (or any other point of absorption, as the skin, peritoneum or other serous cavity) into the absorbing colloid mucous membrane and through this into the blood and lymph. The blood and lymph are ultimately united when they empty into the large veins near the heart. What is the fate of the absorbed water and the dissolved substances? Clearly, two possibilities present themselves: they may be retained in the various cells, tissues and organs of the body, or they may again be given off (perhaps after having suffered antecedent chemical changes) through the various secretions from the body. Under the first of these headings the body cells come to absorb from the blood the amount of water requisite to maintain their normal water content (normal turgor); or, if for any reason the hydration capacity of the hydrophilic colloids in any cell, tissue or organ, or in the organism as a whole has been abnormally heightened, then these absorb more than the usual amount of the proffered water, and swelling to more than normal size give evidence of an œdema in the involved parts. The dissolved substances brought with the water are accepted or rejected by the body cells depending upon whether their content of these is or is not in equilibrium with the concentration of these same substances in the blood. Oxygen, food-stuffs, substances like the salts when present beyond their " physiological " concentrations, various poisons or medicinal agents which by accident or design have gotten into the blood are thus taken up, while carbonic acid and the products of cell metabolism are for the same reason given off.

What water remains above the amount necessary to satisfy the hydration capacity of the body colloids as well as the dissolved substances representing, for example, the products of cell activity, are lost through the secretions. Why this happens and how is our next problem. As the kidney represents both from a qualitative and a quantitative point of view the great

secretory organ of our bodies, we will limit our discussion largely to it. Our remarks upon it may with little modification be applied to any of the other secreting organs, as the skin, the salivary glands, the stomach, etc. The following paragraphs do not presume to give a complete analysis of the physiology and pathology of kidney function; they try, however, to show how the general problem can be broken up into a series of smaller ones. An attempt is made to explain some of these, while others are correlated with problems which still await an answer in physical chemistry.

2. General Remarks on the Structure of a Secreting System in the Complex Organism

The kidney function shows in common with all secretory systems (1) a secretion obtained through (2) a secreting membrane from (3) a source of some kind. In the case of the kidney these terms are synonymous with urine, kidney parenchyma and blood. In their physico-chemical properties they parallel the three phases discussed above as entering into the construction of any absorbing system.

(1) The urine is essentially a watery solution of various electrolytes and non-electrolytes. At times it may be acid, at other times neutral or even alkaline in reaction. Under normal circumstances, as it escapes from the uriniferous tubules, it contains so little colloid material that for our purposes it is negligible. Albumin, mucin, etc., are, of course, present even in normal urine, though in such small amounts that they escape notice when only our ordinary analytical methods are employed.

(2) The secreting membrane through which the urine comes is made up of all the cellular and intercellular elements found between the urine on the one hand and the circulating blood on the other. It is, in other words, the kidney itself. From a histological standpoint this membrane differs somewhat in its different parts. To start with, the membrane consists of a layer of endothelial cells (of the blood capillaries) covered by a layer of the cells of BOWMAN'S capsule, the whole joined together by a certain amount of intercellular substance. While the endothelial cells continue throughout the length of the membrane the additional covering changes, first to the cells of the convoluted tubules,

then to those of the different parts of the loop of HENLE, then to those of the second set of convoluted tubules and finally to the cells of the collecting tubules. The membrane, from a physico-chemical point of view, is colloid in constitution and similar in its general properties to the more solid protein colloids such as fibrin or gelatin. But in no sense are the different portions of the tube made up of exactly the same colloid material, either in a chemical or a physical sense, as clearly indicated by the fact that dyes, for example, do not stain all portions equally.

The membrane, moreover, is *alive*. As we said in discussing absorption, this means that a series of more or less independent chemical and physico-chemical reactions are thereby introduced into our general problem of secretion which demand additional care in the analysis of the whole problem.

(3) The physico-chemical properties of the blood have been previously described. It represents a liquid colloid menstruum in which float the more solid colloid corpuscles, the whole showing the general physico-chemical reactions characteristic of simple proteins.

3. A Model Illustrating Some Phases of Urinary Secretion

Before continuing our main argument it is well to digress here and describe a somewhat crude but quite efficient model of urinary secretion (Fig. 107). Familiarity with it may help to a better understanding of what follows. This model consists of a layer of finely powdered (preferably faintly acid) blood fibrin (*b*) in the bottom of an ordinary calcium chlorid tube (*C*), the outlet of which has been plugged with a little cotton (*a*) to keep the fibrin from falling through. The overflow tube (*c*) keeps the liquid in *C* at a constant level. The whole is fastened in an upright position into a support. Above it are clamped two large separator funnels (*A* and *B*) furnished with stopcocks which permit regulation of outflow.

If now a "physiological" salt solution contained in one of the funnels (m/8 or 0.72% NaCl) is allowed to flow into the calcium chlorid tube in such a way that a constant level is maintained, it is seen to pass through the fibrin (which swells somewhat) and to escape in drops at the lower end of the tube. The rate at which the salt solution escapes (cc. in units of time)

remains constant for indefinite periods of time if the pressure remains the same. If the level of the solution in the calcium chlorid tube is raised, then the "secretion" occurs more rapidly.

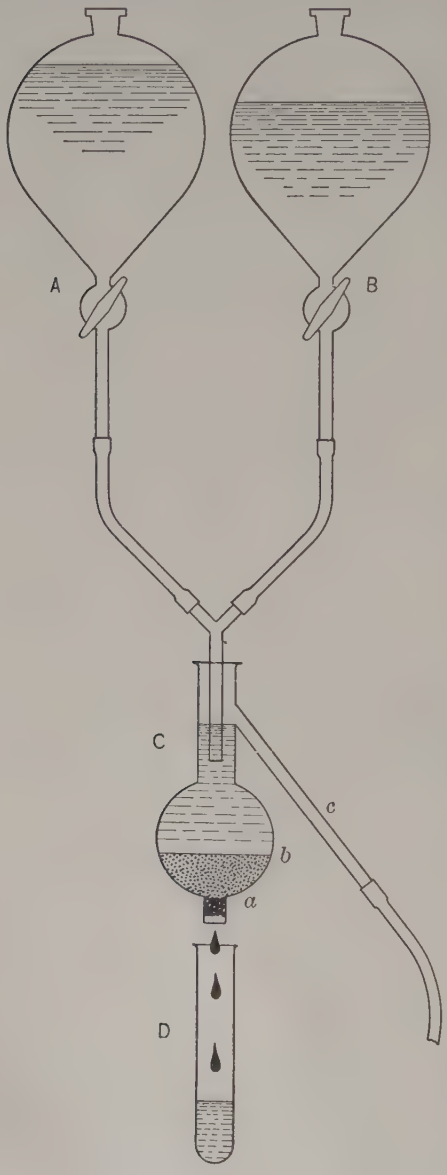


FIGURE 107.

When a dilute acid or a sodium chlorid solution containing an acid is substituted for the pure sodium chlorid solution, the rate of outflow is seen to diminish gradually, and finally, perhaps, to stop entirely. At the same time the fibrin swells and the solution that drips through gives an albumin ring with nitric acid. If the pure sodium chlorid solution is returned to, or enough of this salt, or better, sodium citrate, tartrate or sulphate (or any other of the "saline diuretics") is added to the acid solution, the secretion can be made to recommence, first slowly, then more rapidly, and ultimately the normal, or even a better flow may be obtained. At the same time the albumin ring disappears from the liquid that passes through.

If various non-electrolytes (ethyl or methyl

alcohol, or urea are used in place of the salt solutions, either alone or in combination with an acid, the changes in rate of outflow are scarcely noted, if at all.

The interpretation of these simple facts offers no particular difficulties. The liquids introduced into the calcium chlorid tube escape below after traversing a capillary bed formed by a hydrophilic colloid. Acids of various kinds which make the fibrin swell, decrease the rate of outflow by decreasing the size of the capillaries. The effect of neutral salts and acids on the swelling of fibrin explains why such salts as the citrate, sulphate and tartrate of sodium can make a layer of fibrin permeable to water once more, after it has been rendered impermeable by a pure acid. Albumin appears in the filtrate when it does because the fibrin is (pseudo-)soluble in acid solutions. It becomes less in amount or disappears entirely when enough of different salts is added, because these reduce the "solubility" in acids.

The question now arises whether this model of secretion has anything in common with the physiological and the pathological secretion of urine. I believe it has, though not in as coarse a form as the rough analogy between the model and certain phases of urinary secretion might at first suggest. The model here described was, as a matter of fact, constructed to give tangible evidence to conceptions of urinary secretion which familiarity with the well-known facts of kidney physiology and my own experiments had led me to formulate in my mind. Just how far I think the model simulates conditions observed in experiments on the kidneys will appear later.

We will take up now a series of experimental findings on the secretion of urine which it seems to me can be interpreted, in the light of our knowledge regarding colloids, in a different and simpler way than is generally done. Our discussion will deal separately with the subjects of the secretion of water by the kidneys, and the secretion of substances dissolved in the water. Here too, many writers in physiology and pathology to this day look upon the two as parallel processes. As a matter of fact, they constitute separate problems, and should be dealt with separately.

4. The Output of Water by the Kidney

We are not surprised to find that the secretion of urine ceases (practically) during absolute starvation. If the colloids of the body as a whole are holding on to all the available water, if, in other words, an amount more than necessary to saturate them is not present, then none is left over to be secreted. Only as the tissues undergo gradual consumption during the process of starvation or their colloids suffer changes which decrease their capacity for holding water is any liberated. On the other hand, if a non-thirsting organism (as I will, for short, call one whose colloids are saturated with water) consumes a quantity of water, an amount of urine is excreted (skin and lung ignored), after a variable length of time, which is equivalent to the amount of water that was drunk. (Not to do so means the development of an œdema.) It does not matter how this water was consumed. It may simply have been swallowed or have been experimentally introduced into the gastro-intestinal tract, or it may have been injected into the peritoneal cavity, under the skin, or directly into the blood. By a process of colloid absorption we ultimately reduce all these to one, namely to the presence of water in the blood. What becomes of the water after it has gotten into the blood, as into the venous blood returning from the alimentary tract, is our next problem.

In its transit through the lungs the venous blood coming from the alimentary tract loses the carbonic acid responsible for the increased hydration capacity of its colloids. As soon as this has happened the blood contains more water than the blood colloids are capable of holding, and so this separates off as urine or as some other secretion.[1]

In order to obtain a secretion from the kidney (or any other gland) conditions the reverse of those which favor absorption must be established. Thus, highly venous blood favors absorption, but secretion can occur only when a gland is supplied with arterialized blood (blood low in carbonic and other acids and high in oxygen). Let us now consider some experiments which prove the truth of these contentions.

[1] I have often been asked why the secretion does not occur into the lungs (where the carbonic acid escapes). The truth is that just as much water is lost daily (by evaporation) through the lungs as through the kidneys.

Since the presence of free water in the blood is in my opinion the *sine qua non* for urinary secretion, let us first see what is the effect on secretion of introducing a certain amount of this into the circulation. Since distilled water is destructive to the red blood corpuscles we will inject instead a salt solution. To accomplish such injection without injury to the animal we make use of the apparatus shown in Fig. 108. The graduated cylinder *c* is closed with a soft rubber stopper provided with two glass tubes bent as shown in the diagram and supplied with the rubber tubes *a* and *b* ending respectively in the injection needle *n* and the pressure bulb *d*. When *d* is compressed, any fluid contained in *c* is forced into the delivery tube. After the air is driven out of this the needle *n* is inserted into the ear vein of a rabbit and held in place by two small artery clamps. By pressure upon *d* the fluid may now be injected directly into the animal's circulation at any rate desired. The animal is comfortably tied into an animal holder and the urine is collected through a small soft rubber catheter inserted into the bladder. Unless poisonous substances are injected, the whole procedure does not injure an animal in the slightest, so that it may (with suitable periods of rest between) be used over and over again. No operations are necessary, the animal suffers no pain and therefore there is no need for anesthetics. These prolific sources of error are hence eliminated.

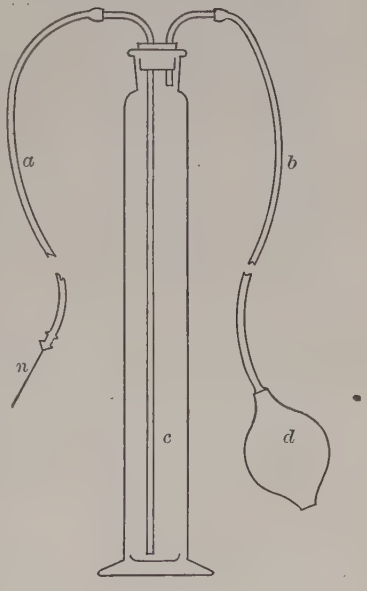


FIGURE 108.

In Fig. 109 are shown the effects on urinary output in a rabbit of injecting intravenously the same amount (125.9 cc.) of differently concentrated sodium chlorid solutions.[1] All the curves

[1] JAMES J. HOGAN and MARTIN H. FISCHER: Kolloidchem. Beihefte, **3**, 304 (1912).

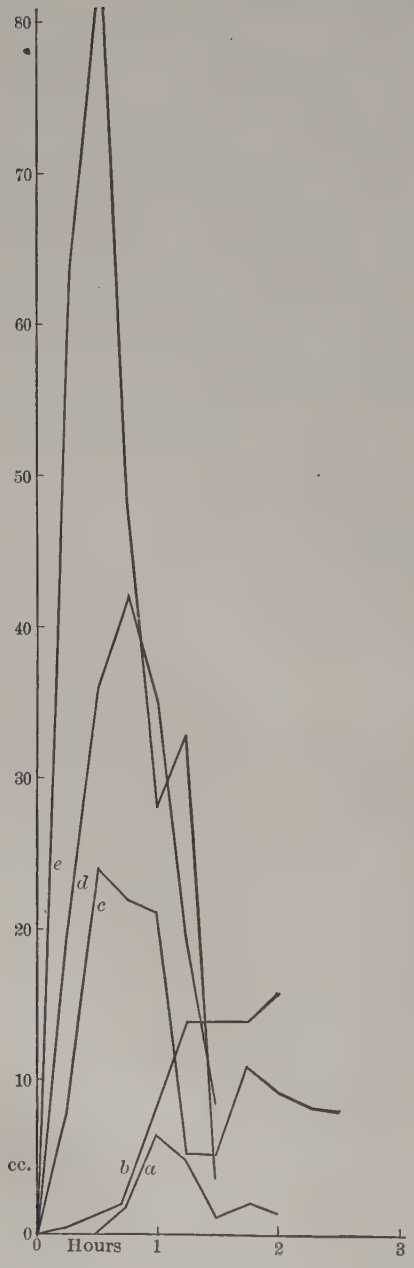


FIGURE 109.

in this figure were obtained from the same animal. The lowermost curve *a* serves as a control and indicates normal urinary secretion. The curves are constructed by plotting time on the horizontal and the amount of urine secreted in fifteen minute intervals on the vertical.

Curve *b* shows the effect of injecting at the uniform rate of 10 cc. every five minutes m/8 (0.729 per cent) sodium chlorid. As is clearly evident such injection soon increases the amount of urine secreted.

Curve *c* shows the effect of injecting an equivalent amount of a sodium chlorid solution alleged to be more nearly "isosmotic" or "isotonic" with the tissue fluids of a rabbit, namely a 0.92 per cent solution. As is readily apparent, in spite of the fact that exactly the same amount of water was injected and at exactly the same rate the urinary output is still further increased. We also notice that the effect of this injection evidences itself sooner upon the secretion.

Curves *d* and *e* show the effects of injecting m/4 (1.459 per cent) and

m/2 (2.909 per cent) sodium chlorid solution. Again, in spite of the fact that the same amount of water has been injected and at the same rate, the loss of water from the body occurs the more rapidly and is the greater the higher the concentration of the injected salt. In these later experiments *little or none of the injected water is retained in the body and if enough salt is injected with the water, the animal loses more water than was injected.*[1]

How are we to interpret these simple facts? As previously emphasized, the whole animal, including his blood and lymph, represents a system of hydrophilic colloids which are saturated with water. This colloid system cannot take up any more water or give off any except as it first suffers chemical or physico-chemical changes which either increase or decrease the capacity of these colloids for holding water. If the system composing the body is saturated with water then it cannot, of course, take up any more, and so if "free" water in the form of a "physiological" (m/8 or 0.729 per cent) salt solution is injected, this cannot be retained, but must escape as urine (or some other secretion).

But why does a stronger salt solution bring about an earlier increase in urinary output and a greater one? It is ordinarily said that this occurs because the salt "stimulates" the kidney in some mysterious way. The explanation is really simpler. The salts decrease the capacity of the body colloids (protein colloids) for water, and this the more the higher the concentration of the salt. The higher, therefore, the concentration of salt in our injection mixture the higher must it be in the blood, and in consequence (after diffusion) in all the tissues of the body. By injecting a strong salt solution we therefore not only inject a certain amount of free water as before, but we make the tissues give off water. This "free" water is then added to that which we injected and it is the sum of the two which appears as urine. *The administration of salt increases the water output through the kidney primarily, not because of any effect upon the kidney but because of an effect upon the body as a whole.* Incidentally, we observe that contrary to much clinical teaching, *sodium chlorid*

[1] These facts are confirmed by the experiments of H. Roger and Garnier: Arch. de Méd. exp., Mai (1913); La Presse Médicale, 885 (1913) who, however, make no attempt to interpret their findings.

administration does not lead to a retention of water in the body and thus to an œdema, but just the reverse. This is in harmony with our previous observations on simple colloids.

Curves *a*, *b*, *c*, *d* and *e* of Fig. 91 have been constructed from the observations contained in Experiments 12, 13, 14, 15 and 16.

EXPERIMENT 12. *Normal Urinary Secretion.*—Belgian male rabbit. Weight 2495 grams. Fed on mixed standard diet. Tied into animal holder and catheterized. No anesthesia.

Time.	Urine in cc.	Remarks.
11.15	.....	Tied down, catheterized.
11.30	—	
11.45	1.6	Clear, yellow, alkaline, no albumin.
12.00	6.4	Same.
12.15	4.8	Same.
12.30	0.9	Same.
12.45	1.7	Same.
1.00	1.3	Same.

Animal released in good condition.

Total urine in the period of one and three-quarter hours, **16.7** cc.

EXPERIMENT 13. *Injection Fluid*: m/8 (0.72 per cent) NaCl.—Belgian male rabbit. Weight 2495 grams. Kept on standard mixed diet of clover hay, oats, corn and greens.

124.9 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. It was estimated that this amount was equivalent to the total volume of blood of the animal. No anesthetic.

Time.	Urine in cc.	Remarks.
2.15	21.5	Tied down, catheterized, injection begun. Urine, clear yellow, neutral, no albumin.
2.30	0.3	Same.
2.45	1.0	Clear, yellow, faintly alkaline, no albumin.
3.00	1.9	Same.
3.15	7.7	Same. Injection stopped.
3.30	14.0	Clear as water, faintly alkaline, no albumin.
3.45	14.0	Same.
4.00	14.0	Same.
4.15	16.0	Same.
4.30	11.2	Same.
4.45	4.8	Same.

Animal released in good condition.

Total urine in two and one-half hour-period since beginning of injection: 84.9 cc.

Urine secreted in the first two hours: **68.9** cc.

EXPERIMENT 14.—*Injection Fluid:* 0.92 per cent NaCl.—Belgian male rabbit. Weight, 2495 grams. Kept on standard mixed diet. 124.9 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every 5 minutes. This amount was estimated as equivalent to the total volume of blood of the animal. No anesthetic.

Time.	Urine in cc.	Remarks.
9.30	2.5	Tied down, catheterized, injection begun. Urine clear, yellow, no albumin.
9.45	7.5	Clear, yellow, alkaline, on albumin.
10.00	24.0	Clear as water, yellow, faintly alkaline, no albumin.
10.15	22.0	Same.
10.30	21.0	Clear as water, neutral, no albumin. Injection ended.
10.45	5.0	Clear as water, yellow, faintly alkaline, no albumin.
11.00	5.2	Cloudy, pale yellow, faintly alkaline, no albumin.
11.15	11.1	Same.
11.30	9.5	Yellow, alkaline, no albumin.
11.45	8.5	Same.
12.00	8.2	Same.

Animal released in good condition.

Total urine in two and one-half hour-period since beginning of injection; 123.3 cc.

Urine secreted in the first two hours: **105.3** cc.

EXPERIMENT 15. *Injection Fluid:* m/4 (1.45 per cent) NaCl.—Belgian male rabbit. Weight 2495 grams. Kept on standard mixed diet. 124.9 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. This amount was estimated as equivalent to the total volume of blood of the animal. No anesthetic.

Time.	Urine in cc.	Remarks.
9.45	.....	Tied down, catheterized, injection begun.
	3.0	Cloudy, yellow, alkaline, no albumin.
10.00	19.5	Clearing, alkaline, no albumin.
10.15	36.0	Clear as water, faintly alkaline, no albumin.
10.30	41.0	Same.
10.45	34.5	Same. Injection ended.
11.00	18.5	Same.
11.15	8.5	Same.

Animal released in good condition. Drinks water at once.

Total urine in the one and one-half-hour period since beginning of injection: **159.0** cc.

EXPERIMENT 16. *Injection Fluid*: m/2 (2.8 per cent) NaCl.—Belgian male rabbit. Weigh 2495 grams. Kept on standard mixed diet. 124.9 cc. of the above solution are injected into ear vein at uniform

rate of 10 cc. every five minutes. This amount was estimated as equivalent to the total volume of blood of the animal. No anesthetic.

Time.	Urine in cc.	Remarks.
10.45	.....	Tied down, catheterized, injection begun.
	4.0	Cloudy, yellow, alkaline, no albumin.
11.00	64.0	Clearing, alkaline, no albumin.
11.15	84.0	Clear as water, neutral, no albumin.
11.30	48.0	Same.
11.45	28.0	Same.
		Injection ended.
12.00	33.0	Same.
12.15	3.5	Same.
12.30	22.0	Same.
12.45	6.0	Same.

Animal released in good condition. Drinks water at once.
Total urine in two-hour period since beginning of injection: **288.5** cc.

The correctness of these views can at once be tested by substituting for the simple salt solutions used above, one in which the water is not "free," but united to a colloid. The natural liquid which has these properties is, if our reasoning is correct, blood itself. We should therefore expect that the injection of no amount of blood would yield any increased flow of urine. That it does not is a familiar fact since the experiments of E. PONFICK[1] and R. MAGNUS,[2] only its interpretation has until now been missing. Curves *a, b, c* and *d* of Fig. 110 and the Experiments 17, 18, 19 and 20, from which they were constructed, show that *the injection of a solution in which all the water is united to a colloid leads to no increase in urinary output.* In these experiments we did not inject whole blood, but blood serum from freshly drawn horse blood obtained under aseptic conditions and permitted to coagulate in an ice box.

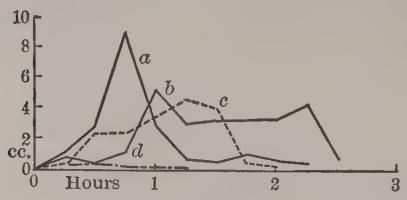


FIGURE 110.

EXPERIMENT 17. *Injection Fluid: The Serum of Horse Blood.*— White Belgian rabbit. Weight 1692 grams. Kept on standard mixed diet.

42.4 cc. of the serum are injected into ear vein at uniform rate of

[1] E. PONFICK: Virchow's Arch., **62**, 277 (1875).
[2] R. MAGNUS: Arch. f. exp. Path. u. Pharm., **45**, 210 (1901).

10 cc. every 5 minutes. This amount was estimated as equivalent to one-half the total volume of blood of the animal. No anesthetic.

Time.	Urine in cc.	Remarks.
10.45	.....	Tied down, catheterized, injection begun.
	4.0	Thick, yellow, alkaline, no albumin.
11.00	1.2	Alkaline, no albumin.
11.07½	.....	Injection ended.
11.15	3.0	Same.
11.30	9.0	Clear, alkaline, traces of albumin.
11.45	3.0	Alkaline, albumin, no casts.
12.00	0.8	Same.
12.15	0.6	Alkaline, less albumin, no casts.
12.30	1.2	Same.
12.45	0.7	Alkaline, faint trace of albumin, no casts.
1.00	0.4	Strongly alkaline, trace of albumin.
1.15	0.8	Same.
1.30	0.7	Same.
1.45	0.5	Same.
2.15	0.5	Same.
2.45	0.6	Same.

Animal released in good condition.

Total urine in four-hour period since beginning of injection: 23.0 cc.

Urine secreted in first two hours: 19.9 cc.

EXPERIMENT 18. *Injection Fluid: The Serum of Horse Blood.*—White and Belgian male rabbit. Weight 1585 grams. Kept on standard mixed diet.

79.1 cc. of the serum are injected into ear vein at uniform rate of 10 cc. every five minutes. This amount was estimated as equivalent to the total volume of blood of the animal. No anesthetic.

Time.	Urine in cc.	Remarks.
11.25	.....	Tied down, catheterized, injection begun.
	2.5	Yellow, alkaline, no albumin.
11.40	1.0	Same.
11.55	0.6	Cloudy, alkaline, no albumin.
12.02	.....	Injection ended.
12.10	1.3	Cloudy, alkaline, trace of albumin.
12.25	5.5	Cloudy, faintly alkaline, albumin, no casts.
12.40	3.5	Same.
12.55	3.5	Slightly cloudy, alkaline, albumin.
1.10	3.5	Alkaline, trace of albumin.
1.25	3.5	Same.
1.55	3.5	Cloudy, alkaline, red blood corpuscles, no casts. (Presence of blood due to traumatic bleeding in the bladder?).
2.25	4.2	Trace of albumin, red blood corpuscles, no casts.
2.55	0.6	Bloody, alkaline, albumin, red blood corpuscles, no casts.

Animal released in good condition.

Total urine in the three and one-half hour period since beginning of injection: 31.1 cc.

Urine secreted in the first two hours: 22.8 cc.

EXPERIMENT 19. *Injection Fluid: The Serum of Horse Blood.*— Himalaya rabbit. Weight 1564 grams. Kept on standard mixed diet. 117.3 cc. of the serum are injected into the ear vein at uniform rate of 10 cc. every five minutes. This amount was estimated as equivalent to one and one-half times the total volume of blood of the animal. No anesthetic.

Time.	Urine in cc.	Remarks.
3.30	.....	Tied down, catheterized, injection begun.
	1.0	Thick, yellow alkaline, no albumin.
3.45	0.3	Same.
4.00	2.6	Thick, yellow, strongly alkaline, trace of albumin.
4.15	2.6	Thick, yellow, strongly alkaline, albumin.
4.30	3.0	Alkaline, albumin. Injection ended.
4.45	4.7	Alkaline, more albumin, some traumatic blood.
5.15	4.2	Alkaline, more albumin, red blood corpuscles.
5.30	0.3	Albumin.
5.45	0.2	Albumin.

Animal released in good condition.

Total urine in the two hour period after beginning of injection: **17.7** cc.

EXPERIMENT 20. *Injection Fluid: The Serum of Horse Blood.*— White male rabbit. Weight 1371 grams. Kept on standard mixed diet. 110 cc. of the serum are injected into ear vein at uniform rate of 10 cc. every five minutes. This amount was estimated as equivalent to one and two thirds times the total volume of blood of the animal. No anesthetic.

Time.	Urine in cc.	Remarks.
4.45	.....	Tied down, catheterized, injection begun.
5.00	4.2	Clear, yellow, acid, no albumin.
5.15	0.5	Clear, no albumin.
5.30	0.4	Clear, faint trace of albumin. Injection ended, animal in good condition.
5.45	0.4	Clear, trace of albumin.
6.00	0.3	Thick, bloody, more albumin.
6.02	.....	The animal dies.

Total urine since beginning of injection: **2.4** cc.

Autopsy: The heart and blood vessels are filled with blood. The peritoneal and pleural cavities are empty.

As we proceed we shall find further experimental evidence for the truth of these views. *The injected blood serum remains in the blood vessels.* To the important physiological and therapeutic consequences of this we shall also return later.

5. On the Colloid-chemical Action of the Diuretic Salts.[1] How the Saline Diuretics Produce Diuresis

Under ordinary circumstances the water output from the kidneys occurs so uninterruptedly and within such "normal" limits that we take it for granted. But in physiology, in pharmacology and particularly in the practical medicine of every day, when for any reason we observe a diminution in urinary output, then a discussion of "diuretics" develops, and of the means of increasing the observed urinary output. In the end certain "saline diuretics" may be prescribed which we know from both physiological and clinical experience to be capable of increasing the urinary output. How such diuretics act has been much debated. As the following shows, *the saline diuretics are nothing but those salts which without being markedly poisonous are the most powerful dehydrants of the body colloids. They owe their action primarily not to any effect upon the kidney, but to an effect upon the body as a whole. By diffusing into the tissues of the body they liberate water from them, and their diuretic activity is but an expression of the amount of water they are thus able to liberate.*

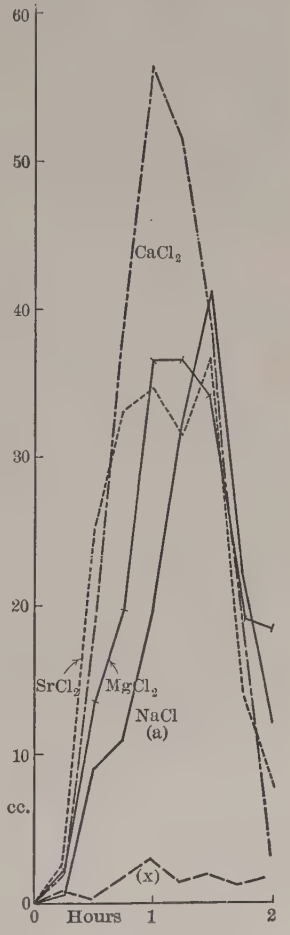


FIGURE 111.

The proof for this is easily brought. We need but make use of the procedure previously employed and inject intravenously into animals equimolar amounts of different salts. When definite volumes (175 cc.) of equimolar solutions are thus injected at a uniform rate into rabbits they

[1] MARTIN H. FISCHER and ANNE SYKES: Science, **37**, 845 (1913); Kolloid-Zeitschr., **13**, 112 (1913).

lead to an increased output of urine which parallels the order in which they dehydrate protein colloids.

For purposes of control Curve *x* of Fig. 111 and Experiment 21 are introduced. This shows the normal urinary output in a rabbit kept on our standard laboratory diet of hay, oats, corn and greens when simply tied comfortably into an animal holder and catheterized.

The remaining curves with their corresponding experiments need no further explanation, for the experimental conditions were the same in all cases. The difference lies in the various salts injected. We adopted the effects of injection of m/4 sodium chlorid solution as a standard for comparison. Curve *a* of Fig. 111 shows the urinary output of a rabbit when injected intravenously with such a solution. If a part of the sodium chlorid is replaced by an equimolar amount of magnesium chlorid, strontium chlorid or calcium chlorid, the urinary output is markedly increased. In place of the 147.4 cc. of urine secreted in the control experiment with sodium chlorid, we now obtained 179.3 cc., 185.5 cc. and 224.2 cc., respectively. *The bivalent metals act as more powerful diuretics than the monovalent, and the order in which they produce diuresis is the same as the order in which they dehydrate simple (protein) colloids in test-tube experiments.* This is shown by the curves of Fig. 111 as well as Experiments 22, 23, 24 and 25, from which they are constructed.

Experiment 21. *Normal Urinary Secretion.*—White male rabbit F. Weight 2639 grams. Kept on standard mixed diet. Tied into animal holder and catheterized. No anesthetic.

Time.	Urine in cc.	Remarks.
10.30	.....	Tied down, catheterized.
	0.6	Thick, yellow, alkaline, no albumin, no sugar, no casts.
10.45	0.8	Same.
11.00	0.2	Same.
11.15	.....	
11.30	3.0	Same.
11.45	1.5	Same.
12.00	2.0	Same.
12.15	1.5	Same.
12.30	2.0	Same.

Animal released in good condition.
Total urine in two-hour period, **10.0** cc.

EXPERIMENT 22. *Injection Fluid:* m/4 NaCl.—White male rabbit B. Weight 2129 grams. Kept on standard mixed diet. 175 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
10.30	.....	Tied down, catheterized, injection begun.
	10.0	Alkaline, no albumin, no casts.
10.45	0.4	Same.
11.00	9.0	Same.
11.15	11.0	Same.
11.30	19.5	Same.
11.45	32.0	Clear as water, alkaline, no albumin, no casts.
11.57½	.....	Injection ended.
12.00	41.0	Same.
12.15	22.5	Same.
12.30	12.0	Same.

Animal released in good condition.
Total urine in two-hour period since beginning of injection, **147.4** cc.

EXPERIMENT 23. *Injection Fluid:* 180 cc. m/4 NaCl+20 cc. m/4 $MgCl_2$.—White male rabbit B. Weight 2146 grams. Kept on standard mixed diet. 175 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
11.15	.....	Tied down, catheterized, injection begun.
	0.5	Yellow, faintly alkaline, no albumin, no casts.
11.30	2.0	Clearing, alkaline, no albumin, no casts.
11.45	13.5	Slightly cloudy, no casts.
12.00	19.5	Same.
12.15	36.5	Same.
12.30	36.5	Slightly cloudy, alkaline, sugar present, no casts.
12.45	34.0	Clear, neutral, no albumin, sugar present, no casts.
1.00	19.0	Same.
1.15	18.3	Same.

Animal released in good condition.
Total urine in two-hour period since beginning of injection, **179.3** cc.

EXPERIMENT 24. *Injection Fluid:* 180 cc. m/4 NaCl+20 cc. m/4 $SrCl_2$.—White male rabbit B. Weight 2170 grams. Kept on standard mixed diet. 175 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
2.45	.....	Tied down, catheterized, injection begun.
	5.0	Yellow, faintly alkaline, no albumin, no sugar, no casts.
3.00	2.2	Same.
3.15	25.0	Same.
3.30	33.0	Slightly cloudy, faintly alkaline, no albumin, sugar present, no casts.
3.45	34.5	Same.
4.00	31.5	Same.
4.12½	.....	Injection ended.
4.15	37.0	Same.
4.30	14.0	Same.
4.45	8.4	Same.

Animal released in good condition.
Total urine in two-hour period since beginning of injection: **185.5** cc.

Experiment 25. *Injection Fluid:* 180 cc. m/4 NaCl+20 cc. m/4 $CaCl_2$.—White male rabbit J. Weight 2214 grams. Kept on standard mixed diet. 175 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
3.15	.....	Tied down, catheterized, injection begun.
	33.0	Thick, cloudy, alkaline, no albumin, no casts.
3.30	2.0	Same.
3.45	18.0	Clearing, neutral, no albumin, no casts.
4.00	38.0	Same.
4.15	56.0	Clear as water, neutral, no albumin, no casts.
4.30	51.0	Same.
4.42½	.....	Injection ended.
4.45	38.0	Same.
5.00	18.0	Same.
5.15	3.2	Same.

Animal released in good condition.
Total urine in two-hour period since beginning of injection, **224.2** cc.
Feces, 16 grams.

The diuretic action of salts with different acid radicals is shown in Figs. 112 and 113. In both figures the sodium chlorid curve, constructed from Experiment 26, is introduced as a control. If the sodium chlorid is entirely or partly replaced by another sodium salt, we find the effect on urinary secretion to be as follows:

Salt.	Urine in cc.
Sodium Chlorid	127.5
Sodium Nitrate	129.4
Sodium Bromid	181.3
Sodium Acetate	182
Di-Sodium Hydrogen Phosphate	184.2
Sodium Di-Hydrogen Phosphate	204.4
Sodium Iodid	237.5
Sodium Sulphate	247

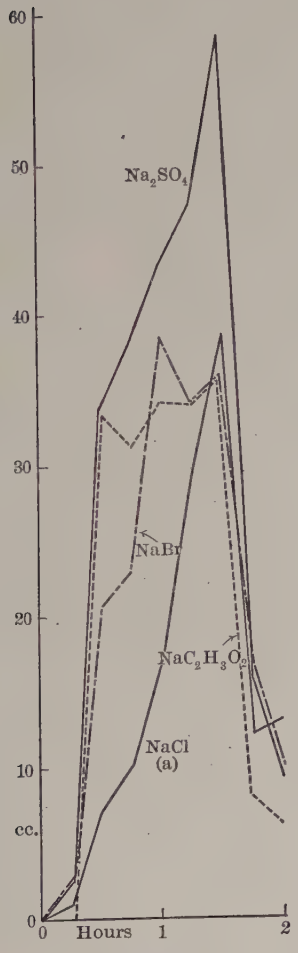


FIGURE 112.

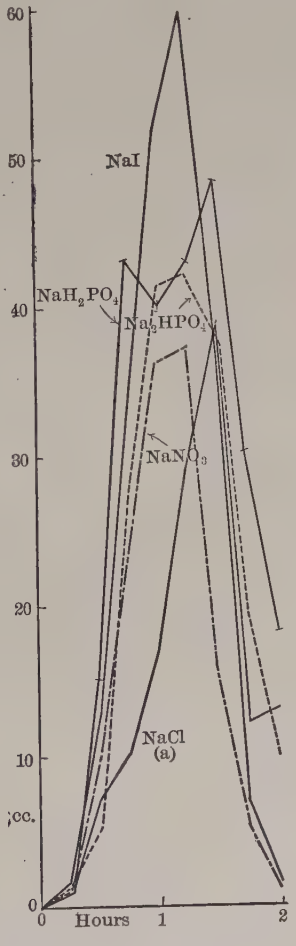


FIGURE 113.

With the exception of the nitrate and the iodid, *the diuretic action of the acid radicals parallels completely their dehydrating effect upon (protein) colloids.* In the amount and concentration employed the nitrate shows a markedly poisonous effect. This is possibly the reason why it stands lower in the series than we should expect. The iodid, on the other hand, stands unexpectedly high. But as we employed a higher concentration of the iodid than of the acetate, the phosphate or the sulphate, the use of a greater absolute amount of the iodid more than compensated for its less powerful action.

The curves of Figs. 112 and 113 are constructed from Experiments 26, 27, 28, 29, 30, 31, 32 and 33.

Experiment 26. *Injection Fluid:* m/4 NaCl. White male rabbit J. Weight 2169 grams. Kept on standard mixed diet. 175 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
12.00	.....	Tied down, catheterized, injection begun.
	5.0	Cloudy, alkaline, no albumin, no casts.
12.15	1.0	Same.
12.30	7.0	Clearing, otherwise the same.
12.45	10.0	Same.
1.00	17.0	Same.
1.15	29.0	Same.
1.27½	.....	Injection ended.
1.30	38.5	Same.
1.45	12.0	Same.
2.00	13.0	Same.

Animal released in good condition.

Total urine in two-hour period since beginning of injection, **127.5** cc.

Experiment 27. *Injection Fluid:* m/4 $NaNO_3$. White and Belgian female rabbit. Weight 1393 grams. Kept on standard mixed diet. 175 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
3.00	.....	Tied down, catheterized, injection begun.
	0.5	Yellow, alkaline, no albumin, no sugar, no casts.
3.15	1.4	Same.
3.30	9.6	Same.
3.45	23.0	Clear as water, otherwise the same.
4.00	36.0	Same.
4.15	37.0	Clear, neutral, trace of albumin, sugar present, red blood corpuscles, no casts.
4.27½	.....	Injection ended.
4.30	16.0	Same.
4.45	5.4	Same.
5.00	1.0	Clear, alkaline, no albumin, sugar present, no casts.

Animal released.

Total urine in two-hour period since beginning of injection, **129.4** cc.

For some hours after its release the animal seems exhausted and takes no food. Next morning is again in good condition.

EXPERIMENT 28. *Injection Fluid:* m/4 Sodium Bromid. White and Belgian female rabbit. Weight 1393 grams. Kept on standard mixed diet.

175 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
11.00	.....	Tied down, catheterized, injection begun.
	1.0	Clear, yellow, alkaline.
11.15	2.8	Yellow, alkaline, traces of albumin, no sugar, many blood cells, many casts.
11.30	20.5	Same.
11.45	23.0	Clear as water, alkaline, faint trace of albumin, no sugar, occasional casts.
12.00	38.0	Clear, alkaline, very faint trace of albumin, sugar present, no casts.
12.15	34.0	Same.
12.27½	.....	Injection ended.
12.30	36.0	Same.
12.45	17.0	Same.
1.00	10.0	Same.

Animal released in sleepy condition.

Total urine in two-hour period since beginning of injection, **181.3** cc.

EXPERIMENT 29. *Injection Fluid:* 100 cc. m/4 NaCl+100 cc. m/4 Sodium Acetate. White male rabbit J. Weight 2419 grams. Kept on standard mixed diet.

175 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
2.45	.....	Tied down, catheterized, injection begun. No urine.
3.00	.....	No urine.
3.15	33.0	Clear, alkaline, no albumin, no sugar, no casts.
3.30	31.0	Same.
3.45	34.0	Same.
4.00	34.0	Clear, alkaline, no albumin, trace of sugar, no casts.
4.12½	.....	Injection ended.
4.15	36.0	Same.
4.30	8.0	Same.
4.45	6.0	Same.

Animal released in good condition.

Total urine in two-hour period since beginning of injection, **182** cc.

EXPERIMENT 30. *Injection Fluid:* 180 cc. m/4 NaCl+20 cc. m/4 Na_2HPO_4. Yellow and white male rabbit. Weight 1444 grams. Kept on standard mixed diet.

175 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
11.45	.....	Tied down, catheterized, injection begun.
	5.5	Thick, yellow, alkaline, no albumin, no sugar, no casts.
12.00	1.5	Clearing, otherwise the same.
12.15	5.2	Same.
12.30	27.0	Same.
12.45	41.0	Same.
1.00	42.0	Clear as water, faintly alkaline, no albumin, trace of sugar, no casts.
1.12½	.....	Injected ended.
1.15	37.5	Same.
1.30	20.0	Same.
1.45	10.0	Same.

Animal released. Found dead in cage next morning.

Total urine in two hour-period since beginning of injection, **184.2** cc.

EXPERIMENT 31. *Injection Fluid:* 180 cc. m/4 NaCl+20 cc. m/4 NaH_2PO_4. Black male rabbit C. Weight 2277 grams. Kept on standard mixed diet.

175 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
11.30	.....	Tied down, catheterized, injection begun.
	8.6	Yellowish-brown, alkaline, no albumin, no sugar, no casts.
11.45	1.8	Same.
12.00	12.5	Clearing, otherwise the same.
12.15	33.5	Same.
12.30	52.0	Same.
12.45	60.0	Clear as water, faintly alkaline, no albumin, trace of sugar, no casts.
12.57½	.....	Injection ended.
1.00	36.0	Same.
1.15	7.0	Same.
1.30	1.6	Same.

Animal released in good condition.

Total urine in two-hour period since beginning of injection, **204.4** cc.

EXPERIMENT 32. *Injection Fluid:* m/4 NaI. Black male rabbit C. Weight 2539 grams. Kept on standard mixed diet.

175 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
3.15	.....	Tied down, catheterized, injection begun.
	4.0	Thick, amber, alkaline, no albumin, no sugar, no casts.
3.30	1.0	Same.
3.45	15.0	Same.
4.00	43.0	Clear, neutral, no albumin, trace of sugar, no casts.
4.15	40.0	Same.
4.30	42.5	Same.
4.42½	.....	Injection ended.
4.45	48.0	Same.
5.00	30.0	Same.
5.15	18.0	Same.

Animal released.

Total urine in two-hour period since beginning of injection, **237.5** cc.

Animal found dead in cage three days later.

Autopsy: Decomposition advanced. Hemorrhagic spots observed in kidney.

Experiment 33. *Injection Fluid.* 100 cc. m/4 NaCl+100 cc. m/4 Na_2SO_4. White male rabbit P. Weight 2670 grams. Kept on standard mixed diet.

175 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
10.30	.....	Tied down, catheterized, injection begun.
	4.3	Clear, amber, acid, no albumin, no sugar, no casts.
10.45	2.4	Same.
11.00	33.6	Clear as water, neutral, no albumin, no sugar, no casts.
11.15	38.0	Same.
11.30	43.0	Same.
11.45	47.0	Same.
11.57½	.....	Injection ended.
12.00	58.0	Clear, no albumin, trace of sugar, no casts.
12.15	16.0	Same.
12.30	9.0	Same.

Animal released in good condition.

Total urine in the two-hour period since beginning of injection, **247** cc.

Salts made up of a powerfully dehydrating base with a powerfully dehydrating acid have, of course, the most effect upon protein colloids. Magnesium sulphate is an example of such a combination. Therefore, if our theory is true, we should expect this salt to produce a greater diuresis than any yet described. That this is actually the case is shown by the curve of Fig. 114 as well as the corresponding Experiment 34. With injection of magnesium sulphate we obtained a urinary output of 300 cc.

EXPERIMENT 34. *Injection Fluid:* 180 cc. m/4 NaCl+20 cc. m/4 $MgSO_4$. White male rabbit J. Weight 2407 grams. Kept on standard mixed diet.

175 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
10.45	.....	Tied down, catheterized, injection begun.
	45.0	Cloudy, yellow, alkaline, no albumin, no sugar, no casts.
11.00	16.0	Same.
11.15	44.0	Almost as clear as water, alkaline, no albumin, trace of sugar, no casts.
11.30	45.0	Clear as water, faintly alkaline, no albumin, much sugar, no casts.
11.45	46.5	Same.
12.00	51.5	Same.
12.12½	.....	Injection ended.
12.15	59.0	Same.
12.30	21.0	Same.
12.45	17.0	Same.

Animal released in good condition.

Total urine in two-hour period since beginning of injection, 300 cc.

The analogies between these various experimental facts on the secretion of urine, and the model previously described and constructed with a view to elucidating some of these facts need no special comment. In our model we have eliminated the colloids of the blood stream, and a colloid reservoir of water corresponding with the water-saturated body colloids, by working with simple salt solutions only. As our considerations have shown, the colloids of the blood and of the tissues generally play a part in urinary secretion in so far as they furnish storage places for water which is liberated under the conditions employed in the described experiments on diuresis. Our model, therefore, illustrates particularly the changes that occur in the kidney (which represents physico-chemically only a much folded colloid membrane). In our model the "secretion" of "urine" is induced through a hydrostatic pressure which forces a liquid through the capillary bed formed by the powdered fibrin. When an acid is brought in contact with the fibrin it swells, closes the capillary pores, and in proportion to the amount of this closure a formerly effective hydrostatic pressure becomes less and less capable, or, finally, even entirely incapable of forcing any liquid through this bed. We can counteract the effect of this acid by various salts, wherein again we find the saline diuretics to be more effective than certain other common salts. Such

a salt as sodium sulphate, of course, makes the fibrin shrink more than an equally concentrated sodium chlorid, and so the former, by increasing the size of the capillary pores, more than the latter favors an increased "secretion" in our model. Matters in the living kidney need not of course, be quite so simple though if the kidney colloids have a physical constitution at all comparable to that of the more solid hydrophilic soap colloids (and much evidence points in this direction) the model which has been described with those to be touched upon later [1] really come closer to the whole truth than might at first sight seem possible.

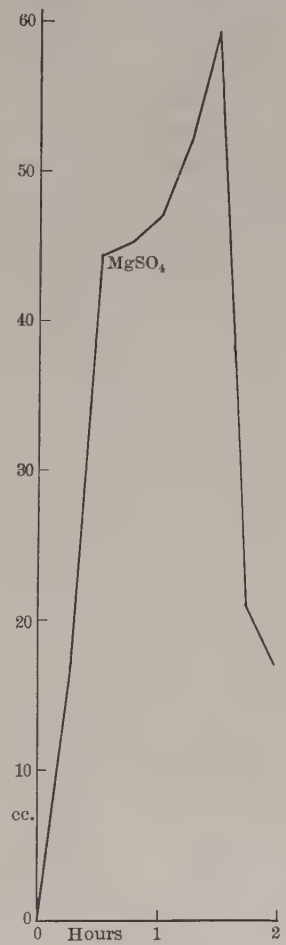


FIGURE 114.

6. On the Colloid-chemistry of Sugar Diuresis [2]

While the various non-electrolytes as compared with the electrolytes do not produce a great dehydration of protein colloids, some of them exhibit considerable activity in this regard, notably the sugars. The experiments which follow reveal their similar dehydrating action upon the whole "living" animal. They therefore do away with the belief of various authors that the dehydrating effects of non-electrolytes on tissues and organisms as a whole, furnish support for the "osmotic" theory of water absorption. At the same time the absurd view is again met that although the colloid-chemical theory explains water absorption in dead tissues its laws do not

[1] See pages 371 and 380.

[2] MARTIN H. FISCHER and ANNE SYKES: Science, **38**, 486 (1913); Kolloid-Zeitschr., **14**, 223 (1914).

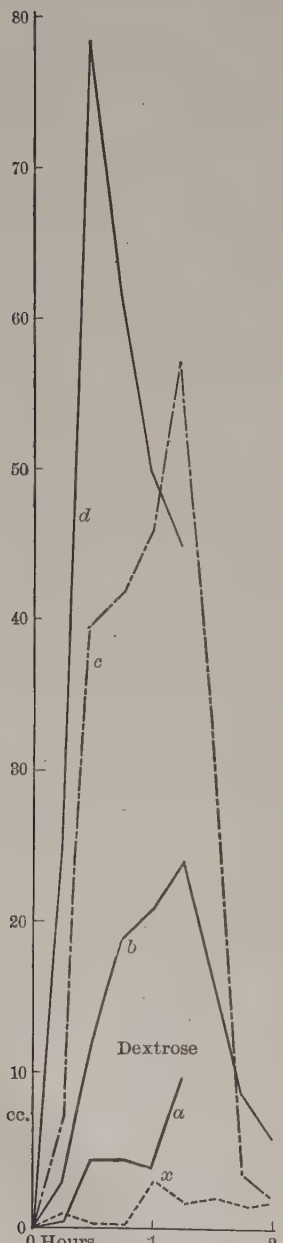


FIGURE 115.

hold for living animals; for it need scarcely be said that our rabbits were alive.

It will now be shown that the diuretic action of the sugars parallels their dehydrating effect on protein colloids, and that like the diuretic salts previously discussed, the sugars owe their action primarily not to any effect upon the kidney, but to an effect upon all the tissues of the body generally. With any sugar the degree of diuresis increases with every increase in the concentration. When we compare the degree of increase in urinary output with that in concentration we find, roughly, that doubling the concentration of sugar more than doubles the urinary output. This is just the reverse of what happens with salt solutions where the lower concentrations produce relatively greater effects than the higher. This difference in the behavior of sugars and of salts upon rabbits parallels their effects upon simple protein colloids. At the same concentration the three sugars produce different degrees of diuresis just as they bring about different degrees of dehydration in gelatin or fibrin, dextrose and levulose standing very close together, while saccharose is far more powerful.

Figs. 115, 116 and 117 present in graphic form the results obtained from Experiments 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45 and 46.

EXPERIMENT 35. *Injection Fluid:* 4/m dextrose. Gray rabbit R. Weight 2500 grams. Kept on standard mixed diet.

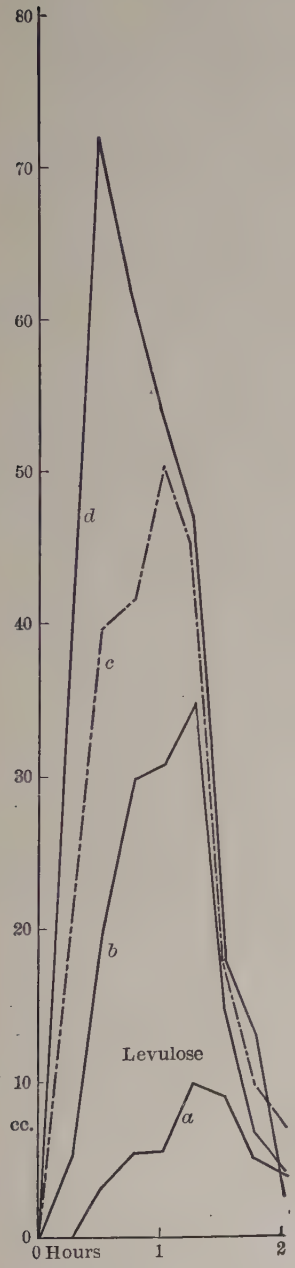


FIGURE 116.

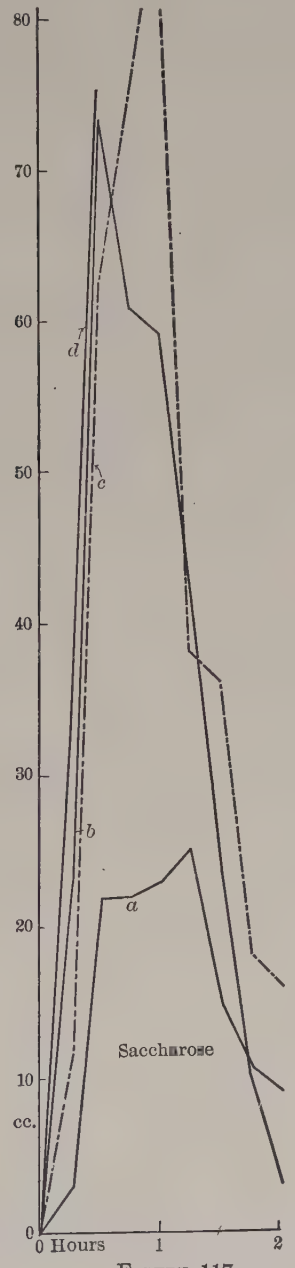


FIGURE 117.

150 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
2.15	.....	Tied down, catheterized, injection begun.
	15.0	Yellow, alkaline, no albumin, no casts.
2.30	A few drops	Same.
2.45	4.5	Same.
3.00	4.5	Same.
3.15	4.0	Clear, neutral, no albumin, no casts.
3.30	10.0	Same.
		Injection ended.

Animal released in good condition.

Total unrine in one and one-quarter-hour period since beginning of injection, **23** cc.

Experiment 36. *Injection Fluid:* m/2 dextrose. White rabbit T. Weight 1600 grams. Kept on standard mixed diet.

150 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
11.15	.....	Tied down, catheterized, injection begun.
	0.5	Yellow, alkaline, no albumin, no casts.
11.30	3.0	Same.
11.45	12.0	Clear as water, alkaline, no albumin, no casts.
12.00	19.0	Same.
12.15	21.0	Same.
12.30	24.0	Same.
		Injection ended.
12.45	17.0	Same.
1.00	9.0	Same.
1.15	6.0	Same.

Animal released in good condition.

Total unrine in two-hour period since beginning of injection, **111** cc.

Experiment 37. *Injection Fluid:* 3/4 m dextrose. Gray rabbit R. Weight 2500 grams. Kept on standard mixed diet.

150 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
2.30	.....	Tied down, catheterized, injection begun.
	30.5	Yellow, alkaline, no albumin, no casts.
2.45	3.0	Clearing, alkaline, no albumin, no casts.
3.00	10.0	Clear as water, alkaline, no albumin, no casts.
3.15	42.0	Same.
3.30	46.0	Same.
3.45	57.0	Same.
		Injection ended.
4.00	33.0	Same.
4.15	3.5	Same.
4.30	2.0	Same.

Animal released in good condition.

Total urine in two-hour period since beginning of injection, **230.5** cc.

EXPERIMENT 38. *Injection Fluid:* m/1 dextrose. Belgian hare. Weight 1534 grams. Kept on standard mixed diet.

150 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
11.30	.....	Tied down, catheterized, injection begun. No urine.
11.45	25.0	Clear, neutral, no albumin, no casts.
12.00	78.0	Same.
12.15	62.0	Same.
12.30	45.0	Same.
12.45	50.0	Neutral, traumatic red blood corpuscles, no casts. Injection ended. Animal released shivering and with teeth chattering.
1.10	.....	Dies.

Autopsy: Everything negative. Cavities empty; tissues dry; petechial hemorrhages in membrane of urethra and bladder. Kidney, pelvis and ureter uninjured.

Total urine in one and one-quarter hour period since beginning of injection, **262** cc.

EXPERIMENT 39. *Injection Fluid:* m/4 levulose. Yellow rabbit Smutty. Weight 2250 grams. Kept on standard mixed diet.

150 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
2.30	.....	Tied down, catheterized, injection begun.
	.....	No urine.
2.45	.....	No urine.
3.00	3.5	Cloudy, alkaline, no casts.
3.15	5.5	Same.
3.30	5.5	Same.
3.45	10.0	Same. Injection ended.
4.00	9.0	Same.
4.15	4.0	Same.
4.30	5.0	Same.

Animal released in good condition.

Total urine in two-hour period since beginning of injection, **41.5** cc.

EXPERIMENT 40. *Injection Fluid:* m/2 levulose. White rabbit B. Weight 1700 grams. Kept on standard mixed diet.

150 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
11.30	.....	Tied down, catheterized, injection begun.
	9.0	Yellow, alkaline, no albumin, no casts.
11.45	5.0	Clear as water, otherwise the same.
12.00	20.0	Same.
12.15	30.0	Same.
12.30	31.0	Same.
12.45	35.0	Same.
		Injection ended.
1.00	15.0	Same.
1.15	7.0	Same.
1.30	4.0	Same.

Animal released in good condition.

Total urine in two-hour period since beginning of injection, **147** cc.

Experiment 41. *Injection Fluid:* 3/4 m levulose. Brown and white rabbit. Weight 1750 grams. Kept on standard mixed diet.

150 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
11.45	.....	Tied down, catheterized, injection begun.
	12.0	Yellow, alkaline, no albumin, no casts.
12.00	22.0	Clear, alkaline, no albumin, no casts.
12.15	40.0	Same.
12.30	42.0	Same.
12.45	50.0	Same.
1.00	45.0	Same.
		Injection ended.
1.15	17.0	Same.
1.30	10.0	Same.
1.45	7.0	Same.

Animal released. Found dead in cage next morning.

Total urine in two-hour period since beginning of injection, **233** cc.

Experiment 42. *Injection Fluid:* m/1 levulose. Black rabbit V. Weight 1530 grams. Kept on standard mixed diet.

150 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
3.15	.....	Tied down, catheterized, injection begun.
	2.0	Yellow, alkaline, no albumin, no casts.
3.30	38.0	Clear, neutral, no albumin, no casts.
3.45	72.0	Same.
4.00	62.0	Same.
4.15	54.0	Same.
4.30	47.0	Same.
		Injection ended.
4.45	17.0	Same.
5.00	12.0	Same.
5.15	2.0	Same.

Animal released. Dies in a short time.

Total urine in two-hour period since beginning of injection, **306** cc.

EXPERIMENT 43. *Injection Fluid:* m/4 saccharose. Yellow rabbit Smutty. Weight 2250 grams. Kept on standard mixed diet.

150 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
2.45	.....	Tied down, catheterized, injection begun.
	6.0	Yellow, alkaline, no albumin, no casts.
3.00	3.0	Same.
3.15	22.0	Clear, neutral, no albumin, no casts.
3.30	22.0	Same.
3.45	23.0	Same.
4.00	25.0	Same.
		Injection ended.
4.15	15.0	Same.
4.30	11.0	Same.
4.45	9.0	Same.

Animal released in good condition.

Total urine in two-hour period since beginning of injection, **130** cc.

EXPERIMENT 44. *Injection Fluid:* m/2 saccharose. Belgian rabbit H. Weight 1800 grams. Kept on standard mixed diet.

150 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
2.45	.....	Tied down, catheterized, injection begun.
	10.0	Yellow alkaline, no albumin, no casts.
3.00	23.5	Clear as water, neutral, no albumin, no casts.
3.15	73.5	Same.
3.30	61.0	Same.
3.45	59.0	Same.
4.00	41.0	Same.
		Injection ended.
4.15	24.0	Same.
4.30	10.0	Same.
4.45	3.0	Same.

Animal released limp and shaking. Next morning alive and well. Five days later alive and well.

Total urine in two-hour period since beginning of injection, **295** cc.

EXPERIMENT 45. *Injection Fluid:* 3/4 m saccharose. Yellow rabbit Sammy. Weight 2250 grams. Kept on standard mixed diet.

150 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
12.00	.....	Tied down, catheterized, injection begun. No urine.
12.15	10.5	Clear, neutral, no albumin, no casts.
12.30	63.0	Same.
12.45	74.0	Same.
1.00	87.5	Same.
1.15	38.0	Same. Injection ended.
1.30	36.0	Same.
1.45	18.0	Same.
2.00	16.0	Same.

Animal released. Found dead in cage next morning.
Total urine in two-hour period since beginning of injection, **343** cc.

EXPERIMENT 46. *Injection Fluid:* m/1 saccharose. Black rabbit U. Weight 1500 grams. Kept on standard mixed diet.
90 cc. of the above solution are injected into ear vein at uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
3.15	.....	Tied down, catheterized, injection begun. No urine.
3.30	32.5	Clear, neutral, no albumin, no casts.
3.45	75.0	Same.
4.00	56.5	Same.
4.05	.....	Animal dies.

When we compare the diuretic action of the sugars with that of the salts we note the same interesting differences as when these two classes of substances are compared in their effect upon the dehydration of protein colloids. Thus, when the same amount of differently concentrated salt solutions (sodium chlorid, for example), is injected intravenously[1] a *relatively* greater effect is produced by the weaker solutions than by the more concentrated, while just the reverse is the case when the sugars are used. This is clearly apparent in the following table:[2]

[1] See page 331: also the first edition of "Œdema" and JAMES J. HOGAN and MARTIN H. FISCHER: Kolloidchem. Beihefte, **3**, 385 (1912). MARTIN H. FISCHER and ANNE SYKES: Science, **37**, 845 (1913); Kolloid-Zeitschr., **13**, 112 (1913).

[2] It should be remembered that owing to dissociation m/8 NaCl solution is "osmotically" almost equivalent to an m/4 solution of a non-electrolyte.

NaCl.	Dextrose.	Levulose.	Saccharose.
m/8 68.9 cc.	m/4 23 cc.	m/4 40 cc.	m/4 130 cc.
m/4 159 cc.	m/2 111 cc.	m/2 147 cc.	m/2 295 cc.
.....	3/4 m 230.5 cc.	3/4 m 231 cc.	3/4 m 343 cc.
m/2 288.5 cc.			

The table also shows how tremendously saccharose dehydrates. Easy as it is to understand on a colloid basis these differences between the sugars or between the sugars and the electrolytes, equally impossible is it to interpret them or any "osmotic" ground.

With these experiments we think that the colloid-chemical theory of water absorption and secretion by protoplasm has answered the last objections of those who oppose its claims to be considered the dominant if not the only factor in this problem.

We believe that on the basis of the dehydrating effect of dextrose upon the tissues can be understood the dryness of the diabetic's tissues and his thirst, as well as the increased urinary output observed resulting from the excessive consumption of water in response to this thirst. A therapy which decreases the amount of circulating sugar in the diabetic organism (without increasing an "acidosis")[1] decreases thirst, water consumption and urinary output.

7. Discussion of the Mechanism of Water Secretion by the Kidney. Some General Conditions Influencing Water Output. Diuretics of the Second Order.

In the evidence thus far presented, which has shown that an output of water by the kidney is possible only as free water is brought to it and in proportion to the amount of water thus brought, we have tacitly assumed that the kidney will always be capable of secreting the water when thus offered it just as in the

[1] What annoys and what kills a diabetic is not generally understood by even the recognized authorities who write on this subject. Thirst and polyuria are annoying and are controlled by controlling the starch and sugar intake of the individual; an acid intoxication dependent upon improper utilization or too great intake of fat is what kills and too great carbohydrate restriction is more to be feared in this connection than the reverse. See the remarks on "acidosis" on page 780. Also MARTIN H. FISCHER: Practical Urinalytic Methods and their Significance in Tice's Practice of Medicine **1**, 423, New York (1920).

model of urinary secretion previously described. We have, in a certain sense, committed ourselves to the view that the secretion of water is a relatively passive affair in that the kidney parenchyma acts as a mere filtration membrane through which the water is squeezed under the influence of the blood pressure. In secreting the water, the kidney need not, however, play such a purely passive rôle. It is held by various authors that in order to transport the water from the blood out into the uriniferous tubules the kidney does work. If this be true then in order to get a normal urinary output the kidney must not only have free water at its disposal, but must also be able to do the necessary secretory work. We have now to discuss the evidence which has been brought forward to support these views.

The proofs commonly adduced to show that the kidney in secreting water actually does work are as follows: there is, first, the old observation that the venous blood returning from an active kidney as well as the urine coming from it have a higher temperature than the arterial blood entering it. Second stand the findings of J. Barcroft and T. G. Brodie [1] that an actively secreting kidney uses more oxygen and gives off more carbonic acid than a resting one, and that the amount of oxygen thus consumed and the amount of carbonic acid thus produced rises hand in hand with the amount of water secreted. Thirdly, E. Heilner [2] has found that when the urinary output in starving dogs and rabbits is increased by forcing water the carbonic acid elimination is increased. To use a homely simile, such observations are intended to prove that fuel is consumed in order to get the energy necessary for a separation of water from the kidney. As in any machine which makes possible such energy transformations many totally different causes may interfere with its smooth running, so also in the kidney many different and apparently disconnected agencies may serve to interfere with the normal energy transformations which permit a kidney to transport the free water offered it in the blood over into the uriniferous tubules. Let us for a moment consider some of these.

As the quantitative and qualitative output from a machine is dependent upon the quantity and nature of the materials fed

[1] J. Barcroft and T. G. Brodie: Journal of Physiol., **32**, 18 (1904); ibid., **33**, 52 (1905).

[2] E. Heilner: Zeitschr. f. Biol., **49**, 373 (1908).

into it, so also the secretion of urine by the kidney is dependent in a striking way upon *the circulation*. Not only can the "normal" secretion of urine be increased through changes in the circulation, but it can still more strikingly be decreased. From histological studies, and, on the whole, very hypothetical reasonings, W. Bowman (1842) first laid stress on the importance of the *pressure* under which the blood flows through the kidneys as a factor in determining the secretion of urine. This pressure idea was further developed and given an experimental basis by Carl Ludwig (1884) and his pupils. Through their work considerable evidence was advanced to show that changes in blood pressure, no matter how induced, are always followed by changes in the amount of urine secreted, and, on the whole, in this sense, that an increase in blood pressure is accompanied by an increased urinary secretion, while a decrease in blood pressure is followed by an opposite result. This long-accepted belief met a setback in the critical studies of R. Heidenhain,[1] who showed that the parallelism between blood pressure and urinary secretion is by no means absolute. Not only does interference with the outflow of venous blood from the kidney—a condition associated with an increase rather than any decrease in blood pressure—lead to a fall in the amount of urine secreted easily equal to the fall encountered after interference with the arterial influx of blood, but various diuretics which do not alter the blood pressure are known to bring about a decided increase in urinary secretion. (Some of the saline diuretics belong in this group, the behavior of which we have already discussed.) Heidenhain maintained that the experimental facts available in his day were best harmonized by saying that the *velocity* with which the blood passes through the kidney determines the amount of urinary secretion. But further than this he did not go with any mechanical or, to put it more generally, physico-chemical concept of urinary secretion.

In place of the teaching of Ludwig that a secretion of urine is primarily dependent upon a blood pressure, or Heidenhain's belief that the velocity with which the blood passes through the kidney is of primary importance, the experiments and clinical observations at hand on this subject are best interpreted by

[1] R. Heidenhain: Hermann's Handbuch d. Physiologie, 5, 309, Leipzig (1883).

saying that *the normal urinary secretion is absolutely dependent upon an adequate oxygen supply to the cells constituting the parenchyma of the kidney. Any interference with this oxygen supply leads to a decrease in urinary secretion even to the point of absolute and permanent stoppage. Through a particularly favorable oxygen supply to the kidneys the secretion of urine may be increased above that ordinarily considered "normal."*

This interpretation meets with no experimental objections. Nature has seen to it that the kidneys shall not lack facilities for a plentiful supply of oxygenated blood by endowing them with strikingly large renal arteries. Any considerable interference with the oxygen supply to the kidney is followed by a drop in urinary secretion. It does not matter how such an interference is brought about. It may be brought about through a change in the action of the heart itself, such as a decrease either in the number or the force of the heart's contractions or both (vagus stimulation, myocarditis, valvular heart disease, dilatation). Or the deficiency in oxygen supply to the kidneys may be brought about through hemorrhage or through stimulation of vasomotor nerves whose effect tends, in the aggregate, to decrease the amount of oxygenated blood passing through the kidneys. Most effectively can the oxygen supply to the kidneys be diminished to any degree or be cut off entirely through compression of the renal artery from without (experimental ligation, clamping, tumor) or occlusion from within (arteriosclerosis, experimental or clinical embolism). The same result is accomplished if the outflow of blood through the renal veins is sufficiently impeded (experimental ligation, tumor, passive congestion due to heart disease).

An adequate oxygen supply to the kidney, on the other hand, favors the secretion of urine. This is evidenced by the fact that the removal of the various conditions outlined above (provided they have not acted too long) is followed by a reestablishment of the urinary secretion to normal. When special efforts are made to increase the oxygen supply to the kidneys, as by ligating several of the larger arteries that pass off the aorta, or by stimulating vasomotor nerves which tend to increase the quantity of oxygenated blood passing through the kidneys, a secretion of urine in excess of that considered normal may be obtained. On the other hand, the most liberal supply of poorly oxygenated

blood to the kidneys even without any other disturbance in the circulation (such as variations in blood pressure) is incapable of maintaining a normal secretion of urine even for a little while.

On the basis of these facts we shall now be able to discuss and to understand the mode of action of certain drugs, exclusive of the saline diuretics, which are capable of increasing the output of water through the kidney. *This second type of diuretic owes its action primarily to its power of favoring the oxygen supply to the kidney.*

It is readily appreciated that in liberating water from a tissue its degree of swelling is reduced. Pressure upon the blood vessels lying within an organ is thereby removed and a better blood flow through the organ favored. Secondarily, therefore, a diuretic salt also brings about a better blood supply to all the organs of the body, including the kidney. On the other hand, the diuretic drugs of the second order in favoring a better oxygen supply to the tissues of the body favor the removal of the acid products of normal and abnormal metabolism, and so incidentally they further diuresis by furnishing " free " water.

We are also familiar with drugs which can decrease the output of water from the kidney. They act in a way the opposite of the diuretics of the second order. We can best begin our discussion with them.

It is a familiar fact that after the administration of morphin or atropin or of chloroform, ether or alcohol, in any considerable amounts, there is always a fall in urinary secretion that may at times amount to complete suppression. It is possible for these substances to lead to such suppression through action upon the kidneys alone. Under ordinary circumstances such a purely local action is, however, not to be anticipated. In fact, it is perfectly possible for a temporary suppression of urine to follow, say, a general anesthetic, without any changes in the kidneys themselves. *The administration of all these anesthetics and of certain alkaloids is accompanied by such a state of lack of oxygen in the tissues of the body generally, as we have before described for isolated organs.* In consequence of this, the capacity of the colloids of all the tissues of the body (including the blood and the lymph) for holding water is increased above that considered normal. After administration of any of these drugs *the body generally, therefore, is holding on to its water with special avidity, so*

that none is left over to be free in the blood and so be excreted through the kidneys. This condition of the tissues after an anesthetic or a dose of morphin, for example, is evidenced not only by the lack of urinary secretion, but by the thirst complained of by the patient. As the patient gets over his anesthetic his urinary secretion not only comes up, but his thirst disappears, even though no water has been given.

To get the described results it will be remembered that considerable amounts of these various drugs have to be administered. Such doses lead to a state of lack of oxygen in the tissues. *Small* doses of ether, alcohol, etc., *increase* the urinary output. In trying to say how this effect is brought about we have to remember the favorable conditions for secretion that are induced in the kidneys when these are given plenty of oxygen (while at the same time their carbonic acid is being rapidly carried away). Such conditions are brought about through the increased frequency and force of the heart beat, the more rapid breathing and the vasodilatation that are induced by *small* doses of these drugs. *A large part of the diuretic action of caffein and its various derivatives, as well as of digitalis, can also be understood on this basis.* The drugs which make for an increased oxygen supply and a favored carbonic acid removal from the kidneys do the same for the body tissues generally. A *decreased* capacity of all the body colloids for holding water is, therefore, a natural result under such circumstances, in consequence of which water is liberated into the blood. This water then becomes available for urine. A dose of caffein or digitalis, therefore, not only puts the kidneys into a condition which favors the secretion of water by them, but at the same time aids in furnishing them water through an indirect effect upon the body colloids generally.

These facts are of the greatest importance when we approach the practical problems of medicine, and we shall, therefore, return to discuss them further when we take up nephritis.[1]

8. Historical and Critical Remarks on Urinary Secretion

We may apply a test to the reasoning of the preceding paragraphs by considering a few of the large number of valuable experimental studies available on the secretion of water by the kidney in the light of the ideas developed above. While the

[1] See page 667.

laboratory facts adduced by different authors harmonize well with each other their interpretation has been warmly debated.

Let us begin by considering the results that have been obtained when various salt solutions have been injected directly into the blood. When a ("physiological") 0.9 per cent sodium chlorid solution is injected into a rabbit, a secretion of urine is obtained which quickly equals the amount of salt solution infused. If a somewhat stronger salt solution is employed, more urine is secreted than is infused, and this difference between amount injected and amount excreted becomes the greater the higher the concentration of the sodium chlorid in the injection fluid. If the injections are very large, or are carried on for a long time, the *absolute* differences between amount infused and amount secreted remain, but the *relative* become less and less apparent.[1] If no time limits are set upon the experiment, the end results become somewhat complicated (though not confusing), owing to the fact that the animal develops the symptoms and signs of a general œdema. This œdema is due to the oxygen want from which the animal suffers whenever these great injections of salt solution are continued sufficiently long.

Isosmotic solutions of the chlorids, bromids and iodids of sodium or potassium bring about approximately the same excretion of urine.[2] When, however, equally concentrated solutions of the various saline diuretics (phosphate, sulphate, tartrate or citrate of sodium) are injected, a much greater secretion of urine is obtained.[3]

How are these various experimental findings to be interpreted? Let us first call attention to the important experimental error that is introduced into any of these experiments if an anesthetic is used. When enough is used to produce anesthesia, a lack of oxygen in the tissues and a retention of some of the liquid infused may be expected to follow. The effect of an infusion is divisible into two parts: first, the effect of the water injected; second, the effect of the salt. Other things being equal, we may expect

[1] See MARTIN H. FISCHER: University of California Publications, Physiology, **1**, 107 (1904).

[2] VON LIMBECK: Arch. f. exp. Path. u. Pharm., **25**, 89 (1888).

[3] MAGNUS: Arch. f. exp. Path. u. Pharm., **44**, 68 and 396 (1900); Ueber Diurese, Heidelberg (1900). TORALD SOLLMANN: Arch. f. exp. Path. u. Pharm., **46**, 13 (1901). B. HAAKE and K. SPIRO: Hofmeister's Beiträge, **2**, 149 (1902).

the water to behave, so far as diuresis is concerned, just as this behaves when water only is injected. The salt injected has an effect upon the kidney and also upon the colloids of the body generally, including those of the blood and lymph. As the chief salt of the body fluids is sodium chlorid, we are not surprised to find that a sodium chlorid solution "isosmotic" with the blood, when injected intravenously, yields in a short time an amount of urine about equal in volume to that of the salt solution injected. If, however, a sodium chlorid solution having a concentration above that of the blood is used, an increased secretion of urine is obtained. This is because the salt acts not only directly upon the colloids of the blood and makes them liberate some of their water, but diffuses into the tissues of the body and makes the colloids here also give up a part of their water. This water is then "free," and can be secreted as urine. The salt also acts upon the colloids of the kidney, making the cells of this organ shrink. This shrinkage of the kidney cells necessarily means a decrease in the pressure exerted upon the blood vessels passing through the kidney, and so a better blood flow through this organ is also favored. The higher the concentration of the injected salt the more water must the body tissues yield up for diuresis (and the better must also be the blood supply to the kidney).

We have no difficulty in understanding why isosmotic solutions of different salts are not equally effective in producing a diuresis. We have become familiar with the unequal effects of different salts on the absorption and secretion of water by colloids. Just as the sulphate, tartrate, phosphate and citrate of sodium are more effective in making fibrin or gelatin give up their water than the chlorid, bromid and iodid of this same metal, so are the former group expected to make the body colloids yield up a greater amount of water for diuresis than the latter. A similar difference of effect is to be expected upon the colloids constituting the kidney. The first-named group must tend to make this "shrink" more than the second.

Let us see how well our theory fares if we apply it to the carefully worked-out experiments of Ernst Frey.[1] This author does not, of course, interpret his experiments as I have taken the liberty of doing for him, but on the more generally accepted

[1] Ernst Frey: Pflüger's Arch., **120**, 66 to 136 (3 papers) (1907).

basis of alterations in the kidney and changes in blood pressure.

FREY finds that when water is given a rabbit by mouth or rectum, or is injected intraperitoneally or into the small intestine, an increased amount of urine is secreted by the kidneys. I would say that this is because the tissues of the rabbit are saturated with water and so none of it is retained. If in place of water, a sodium chlorid solution is injected, the same or even a greater diuresis is obtained. This diuresis is the greater the higher the concentration of the salt solution injected (the amount of fluid injected being the same), just as in our own experiments already described.

The diuresis following the introduction of water does not occur if any anesthetic is administered (morphin, chloral, ether, urethane). This is evidently because the anesthetics all produce a state of lack of oxygen, so that the tissues have an increased capacity for holding water and so do not secrete that which has been absorbed from the alimentary tract or peritoneum. Let FREY'S finding be noted that these anesthetics do not interfere with the *absorption* of water from the gastro-intestinal tract. We are not surprised in the face of our explanation to note that FREY found this retention of water to occur just the same whether he had previously bled the animal or had cut the nerves to the kidneys, or changed the posture of the animal. Not even when he gave phloridzin or salicylic acid in an attempt to " stimulate " the kidneys did he get a urinary flow. According to our ideas of urinary secretion such results are entirely to be expected. None of these procedures affect the hydration capacity of the colloids of the tissues except as some *increase* it.

The continuance of an absorption of water from the gastro-intestinal tract while none is being secreted through the kidneys is easily explained by the increased hydration capacity of the body colloids induced through the effects of the anesthetics.

9. Transition from the Physiological to the Pathological in Kidney Function

One does not pass from the physiological to the pathological in a jump, but insensibly. Thus, the " normal " absorption of water by a cell is ordinarily regarded as subject to well-defined

variations, and yet as we approach the physiological extremes of high normal turgor we are likely to be halted by the information that we have already wandered into the regions of the pathological and are face to face with an "œdema." The same holds true of all other functions. When in physiology we speak of a diminished urinary output we have really gotten into a region which others will call pathology. These paragraphs will show how the physiology and pathology of function as observed in the kidney fade inseparably into each other.

We noted above how a series of most dissimilar disturbances in the circulation to the kidneys are in effect all the same in that they lead to a decreased output of water from the kidney. We have to say now what is the change wrought in the kidneys through the lack of oxygen which is produced in common by all of them. This is a question that we have argued many times before. Not only do we have an abnormal accumulation of carbonic acid in any organ when the blood flow through it is cut down, but through the interference with the oxygen supply to the part we expect an abnormal accumulation and production of various other acids in the affected tissues. Since the tissues contain various (hydrophilic) protein colloids we may expect these to swell if only a source of water is present. It is not surprising, therefore, that oncometric measurements have shown that *every interference with the normal blood supply to the kidneys is followed by an enlargement of the organ, independently of any increase in size that may be due to mere filling of the vessels with blood.*[1] No further comment is necessary to show how these observations and our previously detailed experiments on the œdema of passively congested parenchymatous organs dovetail.[2]

The lack of oxygen induced in the kidneys through circulatory disturbances makes itself felt in the end in the oxidation chemistry of the kidney cells themselves. Now various chemical means are at our disposal by which we can interfere with the oxidations that occur normally in the kidney parenchyma without in any way altering the circulation of the kidney itself. We need mention only the effect of uranyl nitrate and various

[1] See Gottlieb and Magnus: Arch. f. exp. Path. u. Pharm., **45**, 223 (1901). The earlier contradictory results of Starling are open to question. E. H. Starling: Journal of Physiol., **24**, 317 (1899).

[2] See page 268.

other metallic poisons, amyl nitrite, the cyanids and in lesser degree the various anesthetics, such as morphin, chloroform and ether. Every member of this list, which with varying degrees of ease is known to lead to albuminuria, hematuria, partial or complete suppression of urine, enlargement of the kidney and various "degenerative" changes in this organ considered characteristic of "nephritis," is known to interfere with the normal oxidations occurring in living tissues. The bearing that these remarks have on a large number of nephritides, encountered clinically, is apparent not only from the fact that almost every one of the poisons here mentioned has been known to lead to nephritis in man, but by the additional fact that the "toxic" nephritides that appear in the course of various acute infections also belong to this group.

When the oxygen supply to a kidney is cut off sufficiently, or that which passes into it cannot be used properly, albumin, and at times blood, appears in the urine. Such an albuminuria and hematuria may be made to subside if the condition leading to the lack of oxygen is removed after not too long a time. When now, we add to these facts of changes in circulation, increase in the size of the kidneys, progressive diminution in urinary secretion to the point of absolute stoppage, albuminuria, and hematuria, the further fact that on section the kidney parenchyma appears swollen, grayish, and with kidney markings obscured, we have no difficulty in recognizing that *we are dealing with a series of changes that characterize the ordinary acute parenchymatous nephritis.* To this question we return in detail later, but it is brought up here to emphasize the fact that the changes occurring in these experimentally induced nephritides are in part analyzable, and so help not only toward a theoretical understanding of what is observed in clinical cases of acute nephritis, but in so doing give promise of being of practical worth.

10. The Secretion of Dissolved Substances

We shall enter into the problem of *the secretion of dissolved substances* only sufficiently to point out the illuminating touch given it by the physical chemistry of the colloids. Great pessimism still reigns regarding our ultimate ability to explain, on a purely physico-chemical basis, all the phenomena of secretion.

That such a view is not justified must appear from even the brief remarks that follow.

What has been most difficult to explain in secretion has been its selective character; in other words, the ability of the kidney, for example, to separate from the blood a liquid which has a totally different quantitative and qualitative composition. *Qualitative* differences are for the most part explainable through chemical changes that occur in the secretory cells themselves, whereby substances are produced (such as mucin for example) which do not appear in the blood at all. In other respects a secretion differs only in *quantitative* composition from the blood. This may go to the point of having almost entirely absent from a secretion certain constituents of the blood, as, for example, albumin from the urine. For the most part, however, the secretion contains some substances in higher, others in lower, concentration than the blood. To limit ourselves again to the urine, we need by way of illustration only recall that, under ordinary circumstances, the urine contains less chlorids than the blood, and more sulphates and urea. How are such differences to be explained?

To begin with, it is well to call to mind that a secretion of dissolved substances is possible only so long as water is furnished the living organism. *A secretion of water is necessary before we can hope to have any secretion of dissolved substances.* This is a physiological truth that is utilized daily by the intelligent physician when he orders the drinking of large amounts of water to aid the organism in ridding itself of any poison, as the toxin of an infectious disease, for example. How the secretion of water by the kidney may be made a continuous affair we have learned from our previous discussion. How it must make for a continuous secretion of dissolved substances is apparent from what follows.

Let us recall here our division of the urinary secretory system into its three parts: the blood, the secreting membrane, and the urine, and our brief characterization of the first as a liquid colloid in which various crystalloids are dissolved, the second as a solid colloid also containing various crystalloids, and the third as a watery solution of various crystalloids (practically) free from colloids. Thus far our discussion has shown that under the conditions normally existing in the body no water can be introduced into the blood without getting the secretion of an equal

amount as urine. *And what is secreted as urine is water, and only secondarily do substances come to be dissolved in it, so that it assumes a chemical composition which permits it to be characterized as urine.* Let us see now what must happen if some soluble [1] (or pseudo-soluble) substance is introduced into the blood. To simplify the problem and not make our discussion unnecessarily long, let us think of the blood as one homogeneous system, and the urinary membrane as another. Under such circumstances one of three possibilities presents itself from a physico-chemical standpoint. The dissolved substance may distribute itself uniformly throughout the blood and the urinary membrane, or it may be present in either a greater or a less concentration in the urinary membrane than in the blood. Just what will happen is dependent upon the nature of the dissolved substance and the physical and chemical composition of the blood and the urinary membrane at the time. Of greatest importance are such facts as the presence and absence of lipoids, the character of the colloids concerned, and the state of these colloids as determined by the presence of acids, alkalies, salts, or various non-electrolytes. In other words, the laws of partition again come into play. These differences in the distribution of a dissolved substance between the blood and the urinary membrane are rendered strikingly apparent when dyes are used as the dissolved substances.

But this distribution of a dissolved substance between the blood and the urinary membrane represents in the end only a *static* affair, and the secretion of dissolved substances in the urine is a *dynamic* one. It requires no special comment to see now why *only through the continuous secretion of water from the kidney can a continuous separation of dissolved substance from the urinary membrane* (*secretion*) *be rendered possible. The presence of water in Bowman's capsule and in the uriniferous tubules introduces the third phase into our secretory system and breaks down continuously the equilibrium that is trying to become established between the dissolved substances in the blood and the dissolved substances in the urinary membrane.*

The attempt to establish an equilibrium between the dissolved substances in the urinary membrane and the dissolved

[1] The word soluble is used in these paragraphs in its broadest sense, so as to include even the pseudo-soluble (colloid) substances.

substances in the urine (originally only water) as it passes down the uriniferous tubules makes for a diffusion of dissolved substances out of the urinary membrane, and so all the time that water is being secreted by the kidney, tends to destroy the equilibrium, which is trying to become established between the dissolved substances in the blood and the dissolved substances in the urinary membrane. When now we recall the physicochemical fact that when any dissolved substance is offered simultaneously to a liquid colloid, a solid colloid, and water (as is the case in the kidney), an *unequal* distribution of the dissolved substance between the three phases is the *rule*, then we will have no difficulty in understanding why a difference in quantitative composition between the blood, kidney tissue, and urine, so far as dissolved substances are concerned, is also the rule. *Wherefore a "selective" secretion is to be expected rather than to be wondered at.*

Our considerations also indicate how, corresponding with differences in the colloid constitution of the different parts of the urinary tubule, these may show qualitative and quantitative differences in the way in which they secrete the various constituents of the blood. Physiologists have long believed that such differences in function exist.

It is also a matter of indifference to us as to where it is held that the water of the urine is secreted. If this be in the glomeruli, as generally maintained (but not as yet experimentally proved), then we can imagine the water to leach out the various urinary constituents from the secreting membrane as it passes down the uriniferous tubule on its way to the pelvis of the kidney. If water is secreted by several or all portions of the uriniferous tubule, the problem remains, from our point of view, essentially the same.

Our theory also permits of the reabsorption of water, or of dissolved substances, or of both from the fluid passing down the uriniferous tubules as postulated by some observers. It cannot, of course, as yet be accepted that such a reabsorption does occur *physiologically*. That a reabsorption can occur is undoubtedly correct, but the experiments made to furnish evidence for such a belief unquestionably interfere with the normal function of the kidney.

11. A Second Model Illustrating Some Phases of Kidney Secretion

For those interested in the matter, we may now return to a further discussion of the construction of physico-chemical systems which in their behavior mimic what happens in "living" biological secretory systems. To this end I have recently made use of a principle first discovered by THOMAS GRAHAM and of another emphasized chiefly by RICHARD MALY which, in connection with various observations of my own, make easy the laboratory demonstration of certain physiological and pathological facts regarding secretion in general, or urinary secretion in particular, which are ordinarily assumed to be inexplicable in simple physico-chemical terms, and, for the understanding of which, the vague, "vital" forces of protoplasm are too often called into action.[1] It is still a source of wonder to many biological workers that a neutral or alkaline kidney parenchyma can be the mother of an acid urine; that the kidney assiduously "protects" the living animal from being overwhelmed by acid or alkali; that various constituents characteristic of urine are found here in a different proportion from that of these same substances in the kidney parenchyma or in the blood flowing through this; etc. As the following shows, the entire biological fabric is readily reproducible from the simple strands furnished by the concepts of modern colloid chemistry.

§ 1

THOMAS GRAHAM[2] showed many years ago that when any readily hydrolyzable salt, like ferric chlorid, is put into a sac (like parchment) which is permeable to molecularly dispersed substances (crystalloids), but impermeable to more grossly dispersed ones (colloids) and the whole is then hung into water, as shown in Fig. 118 (is subjected, in other words, to dialysis), the following changes occur: Because of the hydrolysis of the ferric chlorid, ferric hydroxid and hydrochloric acid are produced. Since the hydrochloric acid is highly diffusible, it at once begins to escape through

[1] MARTIN H. FISCHER: Jour. Lab. and Clin. Med., 5, 207 (1920).

[2] THOMAS GRAHAM: Quoted by WOLFGANG OSTWALD in Handbook of Colloid Chemistry, translated by MARTIN H. FISCHER, 2d Ed., 233, Philadelphia (1919).

the parchment membrane into the surrounding bath of water. Ferric hydroxid remains behind.

The example here chosen is, of course, not an isolated one. It is characteristic in general of all the hydrolyzable salts. This

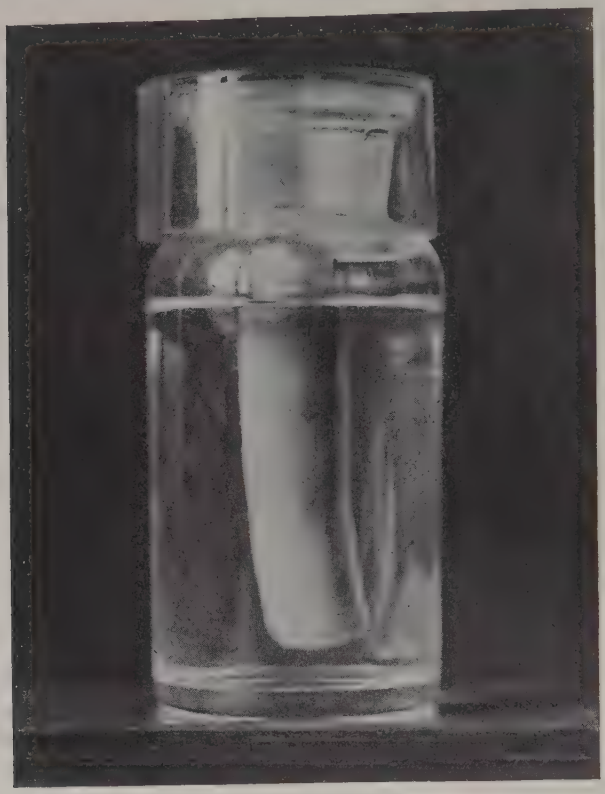


FIGURE 118.

dialysis method was, in fact, used by GRAHAM for the production of many different kinds of non-diffusing "colloids" from the pure solutions of what were originally only molecularly dispersed and highly diffusible salts.

A quantitative study of the *chemical* changes which occur in the experiment just described has been made by S. E. LINDER and H. PICTON.[1] This shows that the proportion of iron to hydro-

[1] S. E. LINDER and H. PICTON: Trans. Chem. Soc., 1909 (1905).

chloric acid steadily increases within the diffusion thimble while it as steadily decreases in the water surrounding the thimble. In other words, the amount of ferric hydroxid increases progressively within the thimble, while the amount of the hydrochloric acid increases without. Iron finally ceases to come out from the internal liquid. The reason for all this is found in the fact that the originally diffusible iron chlorid gradually goes over into a "colloid" iron hydroxid which can no longer pass through the parchment membrane since it contains no holes large enough to let such super-molecular aggregates through.

A quantitative study of the *physical* changes of the thimble contents in this dialysis experiment has been made by N. Sahlbom.[1] By subjecting the solution of iron contained within the diffusion capsule to "capillary analysis" (in which are utilized the principles first discovered by John Uri Lloyd[2] and Friedrich Goppelsroeder[3]) the gradual replacement of the originally highly diffusible iron salt by a non-diffusing colloid one can easily be made a matter of ocular demonstration. If strips of filter paper are simply dipped into the liquid contents of the diffusion thimble on successive days, it is found that, on the first day, both the dispersion medium (water) and the dispersed substance (iron salt) ascend the paper as shown in the first strip of Fig. 119. However, as the change in the thimble contents progresses, the dispersion medium is still found to ascend the paper, but there is a progressive reduction in the height to which the iron salt will go. In the final stages of the exper ment (after the dialysis has been continued for several days) the colloid ferric hydroxid scarcely diffuses at all, coming to rest almost immediately above the surface of the liquid into which the filter paper has been dipped, as shown in the right hand strip in Fig. 119.

This whole experiment may be readily repeated for demonstration purposes in the following fashion. An ordinary parchment paper diffusion thimble (one capable of holding 20 cc. or more) is filled to near its top with a m/5 (about 5 per cent) solution of ferric chlorid ($FeCl_3 \cdot 6H_2O$). The thimble with its contents is

[1] N. Sahlbom: Kolloidchem. Beihefte, **2**, 79 (1910).

[2] John Uri Lloyd: Proc. Am. Pharmaceut. Assoc., **32**, 410 (1884), where references to even earlier studies by him on "capillary analysis" may be found.

[3] Friedrich Goppelsroeder: Capillaranalyse, Basel (1901), where references to his earlier papers may be found.

then suspended in a larger bottle or Erlenmeyer flask as shown in Fig. 118, enough distilled water being poured into the container to bring its level up to the level of the ferric chlorid in the thimble. The distilled water must, naturally, be changed two or more times daily in order to get rid of the products of diffusion.

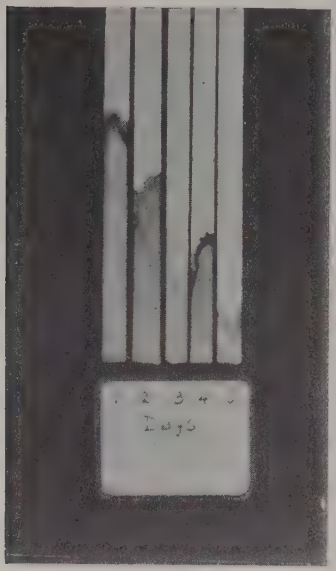


FIGURE 119.

The acid nature of the wash water is readily demonstrated by adding to it some indicator like methyl red. The presence of iron in it is betrayed by the slightly yellowish tinge observable in the first few hours or days of the experiment. If desired, the iron may be demonstrated quantitatively by adding to a given amount of wash water a solution of potassium ferrocyanid. While originally a heavy precipitate is obtained as shown in the left hand tube of Fig. 120, it becomes progressively less until, at the end of four or five days, it disappears entirely. This is shown in the tube marked 5 in Fig. 120. If, now, when the loss of iron has dropped to this zero point, some hydrochloric acid is added to the contents of the diffusion thimble, the iron reappears in the surrounding water as shown in the right hand tube of Fig. 120.

The change to the electronegative ferric hydroxid within the diffusion thimble may be followed by dipping strips of filter paper into the diffusion thimble from day to day and noticing the height to which the color ascends. In the first days the iron salt and the water rise together to a great height, but later (after four to ten days) the water still rises, but the now colloid iron comes to rest just over the surface of the liquid as shown in Fig. 119.

It is important to point out next the analogies which exist between this simple experiment and certain facts of kidney function. If we will call the contents of the diffusion capsule "kidney parenchyma" and the water surrounding the capsule "urine" —the entirely secondary importance of the diffusion capsule will

be pointed out later—the following facts will at once become apparent.

It is obvious, first of all, that there is always derived from the thimble contents a secretion more acid than the medium from which it comes, just as there escapes from the kidney a urine more acid than the tissues themselves. In the later stages of the diffusion experiment an acid secretion is obtained not merely from a

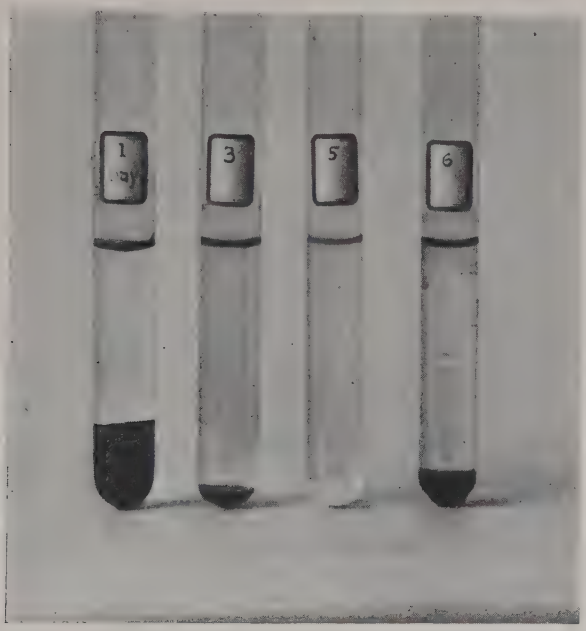


FIGURE 120.

medium which is less acid, but from one which is actually "alkaline." The fact that the ferric hydroxid no longer ascends the filter paper means just this. It is, in other words, an electronegative (alkaline) colloid. But the analogy to kidney physiology and pathology goes further. Ferric hydroxid, except in low concentrations, is a definitely "gelatinous" colloid. Even in the concentrations employed in these experiments it is not an ordinary hydrophobic colloid, but shows distinctly hydrophilic properties. As the argument of the preceding pages has proved, it is this hydrophilic type of colloid which constitutes the bulk of what is

termed protoplasm. The "alkaline" ferric hydroxid is, in other words, the analog of the normal "electronegative" colloids which make up kidney parenchyma.

It is in the later stages of GRAHAM'S experiment when an acid secretion of molecularly dispersed substances containing no iron is being derived from a hydrophilic colloidally dispersed matrix that we have the parallel of what happens in kidney and urine under physiological conditions. The hydrated ferric hydroxid in the presence of traces of salts does not "dissolve" in water (just as no albumin dissolves out of the kidney to appear in normal urine). But if the acid content of the ferric hydroxid is slightly increased, the colloid "dissolves" more easily, shows increased diffusibility and becomes readily miscible with water. In the case of GRAHAM'S experiment the iron now diffuses through the parchment capsule and "appears in the urine." This is analogous to what happens in the kidney under pathological circumstances, as in nephritis.[1] Under the influence of the abnormal production or accumulation of acids (or of similarly acting substances like alkalies, amins, pyridin and urea) in the kidney parenchyma, this not only swells, but shows an increased tendency to diffuse and an increased miscibility with water, and this explains why the material of the colloid matrix, in other words, albumin, begins to appear in the liquid which bathes the parenchyma. The urine, in other words, from which under normal circumstances albumin is absent, now contains such. Accompanying such change, however, there is an increase in the titration or hydrogen-ion acidity of the urine expressive of the increased acid content of the kidney parenchyma. In similar fashion, in GRAHAM'S experiment there is a loss of iron during the first hours and while the acid content of thimble mixture and external fluid is high, to become less and less as the more rapid loss of acid allows the iron to change to a hydroxid and a non-diffusible form. The renewed addition of acid to the colloid iron hydroxid within the thimble again increases the solubility and diffusibility of the iron and at once this manifests itself by a renewed appearance of this metal in the wash water about the diffusion thimble.

The diffusion capsule, it must be clearly kept in mind, is of entirely secondary importance. Even if it were absent, the same results would be obtained, for the parchment thimble only man-

[1] See page 504.

ages in mechanical fashion to keep together the iron solution. Separation through diffusion is the same whether such diffusion is "free" or partially hampered through a colloid membrane.

In the case of a normal kidney the parenchyma itself (the protoplasm of the cells) behaves like the parchment thimble. In nephritis such colloid structures are destroyed and the kidney mixes with the urine just as the non-colloid iron salt would mix with the water, were no parchment thimble present.

§ 2

In order to show that an entirely analogous behavior is observable if a protein is used instead of an iron salt, the following experiment with gelatin was devised. Gelatin shows, like other proteins an increasing tendency to liquefy or "dissolve" (an increased degree of dispersion and an increased tendency to diffuse) in the presence of sodium phosphate as the acid or alkaline content of the phosphate mixture is increased from a given low point.[1] The Erlenmeyer flasks of Fig. 121 contained the following gelatin-phosphate-water mixtures:

1. 50 cc. 2% gelatin+3 cc. m/1 NaH_2PO_4+4 cc. n/1 H_3PO_4 +43cc. H_2O.

2. 50 cc. 2% gelatin+3 cc. m/1 NaH_2PO_4+3 cc. n/1 H_3PO_4 +44 cc. H_2O.

3. 50 cc. 2% gelatin+3 cc. m/1 NaH_2PO_4+2 cc. n/1 H_3PO_4 +45 cc. H_2O.

As shown in previous observations on this gelatin, these mixtures are just liquid to decidedly liquid at 21° C., a fact readily manifest in the photograph. These liquid mixtures were poured into ordinary parchment diffusion capsules and dialyzed against distilled water for a number of days. On the fourth day of the dialysis the gelatin in the diffusion thimble of 3 had become semi-solid, while that in the remaining thimbles was still liquid. On the fifth day the gelatin from the third mixture was solid, that in the

[1] See page 596, also MARTIN H. FISCHER: Science, **46**, 189 (1917); MARTIN H. FISCHER and WARD D. COFFMAN: Jour. Am. Chem. Soc., **40**, 303 (1918).

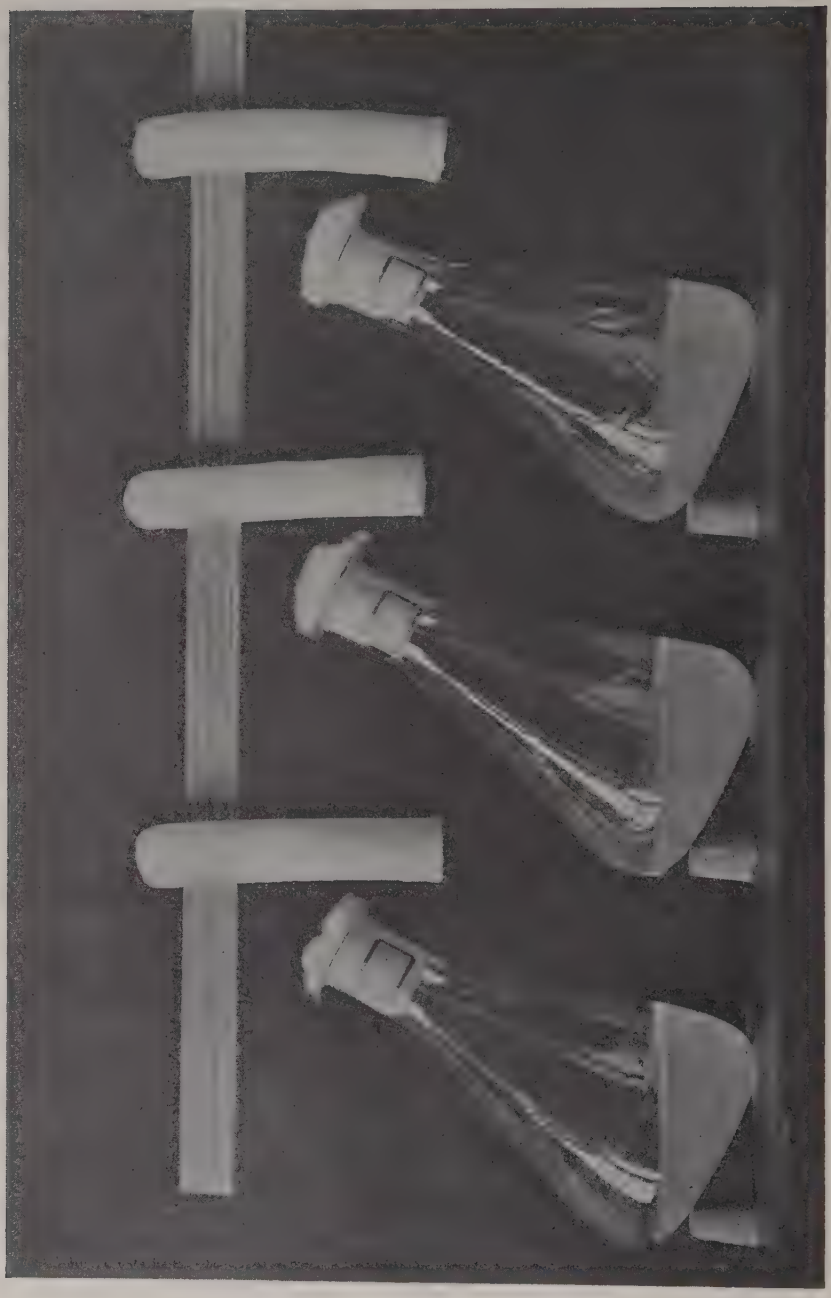


FIGURE 121.

second semi-solid, while that in the first was still liquid. At the end of ten days all were solid.[1]

To understand what has happened it is only necessary to call to mind RICHARD MALY'S [2] classical observations on diffusion. In order to get a physico-chemical counterpart of the production of a secretion (like gastric juice or urine) more acid than its source (the glandular parenchyma or the blood) he studied the separation which occurs when free diffusion or diffusion through a parchment membrane is permitted a mixture of acid with an acid salt or one of an acid salt with a neutral salt, etc. Generally speaking, the more acid constituents of such a mixture leave it first, leaving behind the more neutral compounds. It is this principle which is utilized in the experiment described above. From a phosphate mixture containing phosphoric acid, the phosphoric acid diffuses out sooner than the acid phosphate; while from the acid phosphate itself an acid fraction diffuses out leaving behind disodium phosphate. As this occurs, the previously liquid gelatin becomes more and more viscid until, as " neutrality " is approached, the mixture becomes solid.

The experiment shows in reverse order the state which characterizes the kidney in nephritis and normally. As will be shown later,[3] albuminuria represents a " solution " of the previously insoluble kidney and is brought about through an accumulation in the kidney parenchyma of materials like acids (alkalies, amins, pyridin or urea). The continuance of the kidney in its normal solid state is dependent upon the maintenance in this structure of a reaction more nearly neutral. In the experiment described above this " normal " state of the kidney is represented by the solid gelatin in the diffusion capsule at the end of the experiment; the nephritic state, by the liquid gelatin readily miscible with water with which the experiment was started. While the urine of the carnivora is for most of each day and normally more acid than the kidney parenchyma or the blood, this acidity is greatly increased under the pathological circumstances which are associated with

[1] To reduce liability to infection with liquefying organisms it is well to make up the gelatin mixtures in sterile form, to soak the diffusion capsules in boiling distilled water before use, and to keep the diffusion flasks stoppered with sterile cotton plugs.

[2] RICHARD MALY: Zeitschr. f. Physiol. Chem., **1**, 174 (1877).

[3] See page 507, also MARTIN H. FISCHER: Œdema and Nephritis, 2d Ed., 433, New York (1915), where references to the earlier papers may be found.

" nephritis." These facts, too, may be readily observed in the described experiment.

The more acid nature of the " secretion " in the experiment described above as compared with that of the " parenchyma " (the gelatin mixture) may be observed at any stage of the diffusion by adding some indicator like methyl red or litmus to the capsule contents and to the wash water surrounding the capsule. While I hold that there are serious objections to be raised against the application of indicator methods to definitely colloid systems and to the interpretations which are ordinarily made of such findings[1] it is nevertheless true that the acidity of the wash water gradually falls. While originally, for example, methyl red is turned violently red, this indicator shows only a reddish-brown color when diffusion has been allowed to progress for several days.

12. A Third Model Illustrating Some Phases of Kidney Secretion [2]

We purpose returning in these paragraphs to that half of the secretory process which has to do with the mechanism by which a glandular parenchyma separates *water* from the blood and thus fathers a secretion.

§ 1

If we ignore the entirely purposeless efforts to explain such separation on a " physiological" basis—which amount in essence to nothing more than the statement that a cell secretes because it secretes and that it fails to secrete because it can not—then the attempts to account for what is observed may be divided into two classes. The first of these is the filtration theory originally put forth in purely speculative form by Bowman and later upon an experimental basis by Carl Ludwig and his followers. The second is properly not a theory at all, but really only a critique of the Bowman-Ludwig concept by R. Heidenhain and his successors, who, on the basis of various physiological observations (in which the questions of the secretion of water and the secretion

[1] See pages 765 and 775. Also Martin H. Fischer: Science, **49**, 615 (1919); Chem. Engineer, **27**, 271 (1919).

[2] Martin H. Fischer and George D. McLaughlin: Jour. Lab. and Clin. Med., **5**, 352 (1920).

of various dissolved substances are hopelessly confused) negate the adequacy of the filtration hypothesis. A good illustration of the modern situation is furnished by the work previously cited of T. G. BRODIE and his co-workers,[1] who, from their experiments on urinary secretion, came to the conclusion that the secretion of water by such an organ as the kidney is paralleled by a consumption of oxygen. At times there was also an increased carbon dioxid production. In plainer terms, such a parallelism means that in secreting water the kidney does work, that this work calls for a consumption of energy, and that the greater the amount of work thus done, the greater the consumption of energy. While we have ourselves supported such a view,[2] recent studies[3] on the structure of colloid systems and the analogy existing between these and protoplasm has made us look into the whole problem anew. The experimental findings of BRODIE and his co-workers have, moreover, been drawn in question by the observations of other authors, notably those of J. BARCROFT and H. STRAUB,[4] who noted an even twentyfold increase in water output by the kidney, under the influence of injections of various salt solutions, with *no* appreciable increase in oxygen consumption. As must be apparent, the two observations are mutually exclusive for were they both correct, it would compel the conclusion that to secrete water the kidney must sometimes do work and sometimes not. Is there a less inconsistent way out?

In our opinion there is, provided we will stop confusing the two elements of the secretion of water and the secretion of dissolved substances, and bear in mind the conditions experimentally found necessary for every increase or decrease in the secretion of these two materials and the significance of such conditions in the body of the living animal from a colloid-chemical point of view.

Our previous studies have shown that the conditions making for the *absorption* of water by the colloid-chemical mass which we term a living animal, are the opposite of those which make for the

[1] J. BARCROFT and T. G. BRODIE. Journal of Physiol., **32**, 18 (1904); ibid., **33**, 52 (1905);. T. G. BRODIE and W. C. CULLIS: Journal of Physiol., **34**, 224 (1906); T. G. BRODIE: Harvey Lectures, Phila. (1909); A. R. CUSHNY: Secretion of Urine, 34, 35, London (1917).

[2] See the first and second editions of this volume.

[3] MARIAN O. HOOKER and MARTIN H. FISCHER: Chem. Engineer, **27**, 155, 223, 253 (1919); MARTIN H. FISCHER: Chem. Engineer, **27**, 184, 271 (1919).

[4] J. BARCROFT and H. STRAUB: Journal of Physiol., **41**, 145 (1911).

secretion of this same substance. Thus water is absorbed only as the capacity of the body colloids for holding water is increased by any of various circumstances, while a separation or secretion of water follows as these conditions are reversed. Water is therefore best absorbed in those portions of the alimentary tract (the large intestine) which are bathed by the most venous blood (that richest in carbonic or other acids) while no such absorption occurs in the stomach during the "periods of digestion" when this viscus is supplied with highly arterialized blood. A *secretion* of water, after its absorption into the venous blood, becomes possible as soon as the acid content of this venous blood (carbonic acid under normal circumstances or other acids in states of disease) is diminished on passing through the lungs. At this point water becomes "free" and may be lost through any secretory organ. A first place of loss is in the lung itself, while the other places of loss of general importance are represented by the kidney and the sweat glands of the skin. To make possible a secretion of water, the following conditions must, therefore, be satisfied: (1) "free" water must be brought to the secreting parenchyma, (2) the blood carrying such free water must contain a sufficiently low concentration of various acids (and a sufficiently high concentration of oxygen) and (3) if the secretion of water is to cost the kidney or other secreting gland no work the secreting parenchyma must be " permeable " to the free water and not to the combined.

The previous pages have shown how the experimental data of other authors, as well as our own all support the first two of these conclusions. A water-starved animal is incapable of any secretion; and the injection of any amount of water in combined form (as whole blood, blood plasma or any proper hydrophilic colloid) will not increase any secretion by a drop. Secretion increases and is proportional to the amount of "free" water furnished the secreting organ (in other words, the amount available above that necessary for saturation of the colloids). When secretion-promoting substances like saline diuretics or materials of the type of caffeine and digitalis are used, the mechanism still remains in essence the same. In the first instance, the administered salts dehydrate the body colloids generally, and thus make available free water for secretion, while, in the second instance, they increase cardiac and respiratory efficiency, and by thus increasing the circulation

through the tissues, decrease their content of carbonic and other acids, thus again making for the appearance of the free water necessary for secretion.

These ideas may be applied to such experiments as those of BRODIE and his followers, and BARCROFT and STRAUB. While insisting upon the general parallelism between amount of oxygen consumed and water secreted a study of the individual protocols and foot-notes of even the first named of these authors indicates that he himself failed to discover such parallelism whenever a diuretic salt was administered; and this is the rule in all of BARCROFT and STRAUB'S findings. We would, in our own terms, say that these facts compel the conclusion that the secretion of "free" water does *not* cost a kidney or other secreting organ any work. This conclusion is the logical one demanded by the colloid-chemical theories of absorption and secretion for which we have so long stood, but because such apparently finite experiments and deductions as those of BRODIE stood against us we, too, insisted that water secretion represented an "active" process,[1] and thus failed to find in filtration and the "microcapillary" structure of the colloids (as illustrated in our first urinary secretion model[2]) an explanation of *all* the phenomena observed in a living animal. *If the secretion of water is essentially a filtration process, simple hydrated colloids of proper composition ought to behave like kidney parenchyma. The following experiments show that they do.*

§ 2

We chose for particular study the system, hydrated sodium stearate. For filtration purposes this was cast into cylindrical cups measuring in the moist condition 7.2 cm. transversely by 5.2 cm. high, with walls 1 cm. thick. The cups were made by supporting one calibrated beaker (of 120 cc. capacity) within a second (of 350 cc. capacity) and filling the intervening space with a hot sodium stearate solution. After the material had "set" by being cooled to room temperature, the soap model was removed from the mold and set up for experimental purposes as indicated in Fig. 122 except that the whole was covered so as to prevent un-

[1] MARTIN H. FISCHER: Œdema and Nephritis, 2d Ed., 314, New York (1915).

[2] See page 327.

due evaporation. In the experiments to be described, the filtration properties of the cups were then tested by filling them with 80 cc. of the solution to be filtered. The filtration pressure (the hydrostatic pressure) represented by this volume of fluid is 5 cm.

FIGURE 122.

Water filters through such a soap cup in a fashion remarkably analogous to that observed in the various secreting organs of the body.

1. We tested out first the effects of the concentration of the hydrated sodium stearate system upon the filtration of water through it. The amounts of water which will pass through a sodium stearate cup of different concentrations under the circumstances described for these experiments are indicated in Table XCVI.

These experiments show that the ease with which water filters through a hydrated sodium stearate decreases with every increase in the concentration of the colloid membrane. The filtration capacities of the different soap cups are so strikingly different that they are readily apparent to the naked eye as shown in Fig. 123, which is a photograph of this experiment at its end.

2. It was our next purpose to demonstrate the gross differences existent between the rate at which "free" water will filter through

TABLE XCVI

AMOUNT OF WATER IN CC. WHICH FILTERS THROUGH SODIUM STEARATE CUPS OF DIFFERENT CONCENTRATIONS

Hours allowed for filtration.	Concentration of Sodium Stearate cup.					
	m/2	2/5 m	3/10 m	2/10 m	m/10	m/20
2:45	0	0	0	0	3	27
4	1	2	1	1	6	34
5	1	3	3	2	8	42
6	2	3	4	2	10	46*
8	3	5	5	4	14	62
24:15	3	10	11	12	36	96
Neutralization value in cc. n/10 H_2SO_4 of whole filtrate	.1	.5	.6	.6	1.2	1.4
Neutralization value per cc. of filtrate	.033	.050	.054	.050	.033	.014

* 25 cc. more H_2O added to this cup.

TABLE XCVII

AMOUNT OF WATER IN CC. WHICH FILTERS THROUGH m/10 SODIUM STEARATE CUPS WHEN "FREE" OR "COMBINED" WITH HYDRATABLE COLLOID

Hours allowed for filtration.	Composition of liquid being filtered.	
	H_2O	m/1 Sodium Oleate
:30	2	0
1:15	6	0
2:15	9	0
3:15	15	0
4:15	19	0
5:15	23	0
20:00	30	0

TABLE XCVIII

AMOUNT OF WATER IN CC. WHICH FILTERS THROUGH m/10 SODIUM STEARATE CUPS FROM PURE WATER OR SOLUTIONS OF SODIUM CHLORID OF DIFFERENT CONCENTRATIONS

Hours allowed for filtration.	Composition of liquid being filtered.			
	H_2O	m/8 NaCl	m/4 NaCl	m/1 NaCl
4	10	13	15	20
7	16	19	22	27

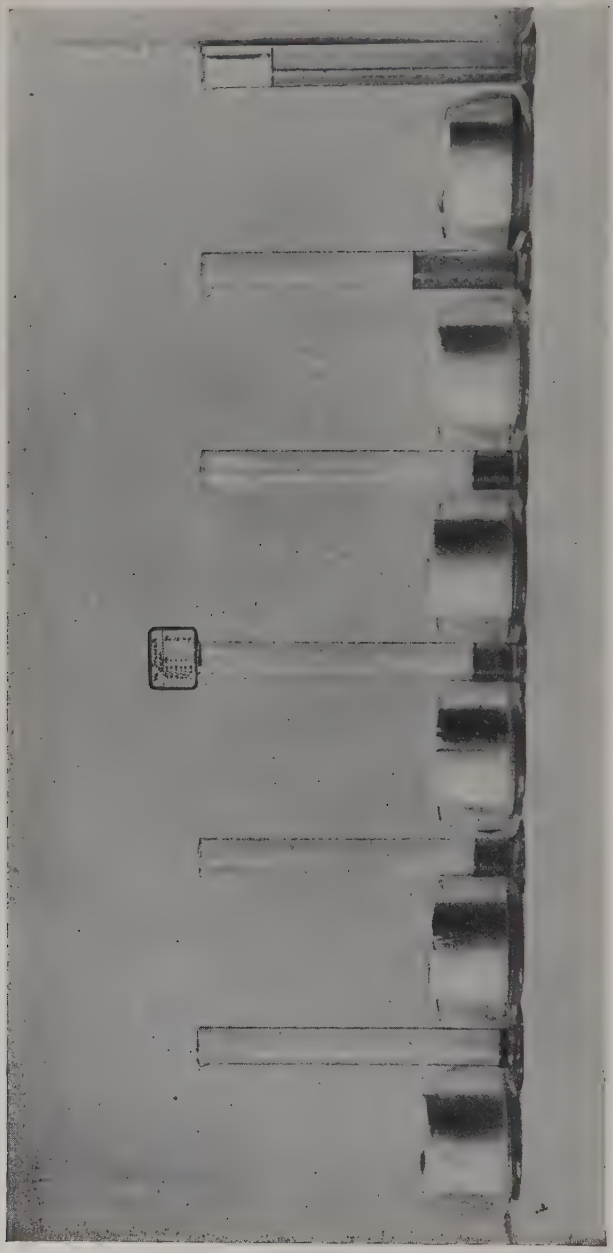


FIGURE 123.

such a colloid cup and combined water as represented by a liquid colloid which in its physical constitution may be compared with blood. To this end we compared the filtration of water with that of a molar "solution" of sodium oleate. Since in the previous series of experiments m/10 sodium stearate cups had yielded a good average filtration rate we chose these for this experiment and the subsequent ones.

This experiment shows that water when combined with a hydrophilic colloid fails to come through a hydrated soap just as urine fails to come from blood when this contains no "free" water. That it is nothing specific about the sodium oleate which makes the filtration of water impossible, but merely the fact that the water is bound to the sodium oleate, is proved by the fact that mere dilution of the sodium oleate, sufficient to guarantee the presence of free water, at once allows some liquid to filter through. Its amount in no instance, however, equals that when pure water is used.

3. These colloid soap cups may be used to illustrate even the biological action of the various salines in increasing secretion. The saline diuretics owe their effects[1] to a dehydrating action upon the hydrophilic (protein) colloids of the body in general and upon those of the kidney in particular. By dehydrating the proteins of the body in general, they furnish "free" water for the kidney to secrete, while through such action upon the kidney specifically, they not only exhibit this function, but through it, obviously, the diameter of the capillaries must be increased which must be existent in the glandular parenchyma if mere filtration is presumed to be the mechanism by which free water is squeezed off from the blood.

The effects of the salines are different both as to their concentration and their kind. Table XCVIII illustrates upon colloid soap how the "diuretic" effect of any salt is increased with every increase in its concentration.

The results of this experiment at the end of 7 hours are shown in Fig. 124.

4. Table XCIX illustrates the difference in effects when equally concentrated (equimolar) solutions of salts possessed of a common acid but different basic radicals are filtered through a series of cups.

[1] See page 339.

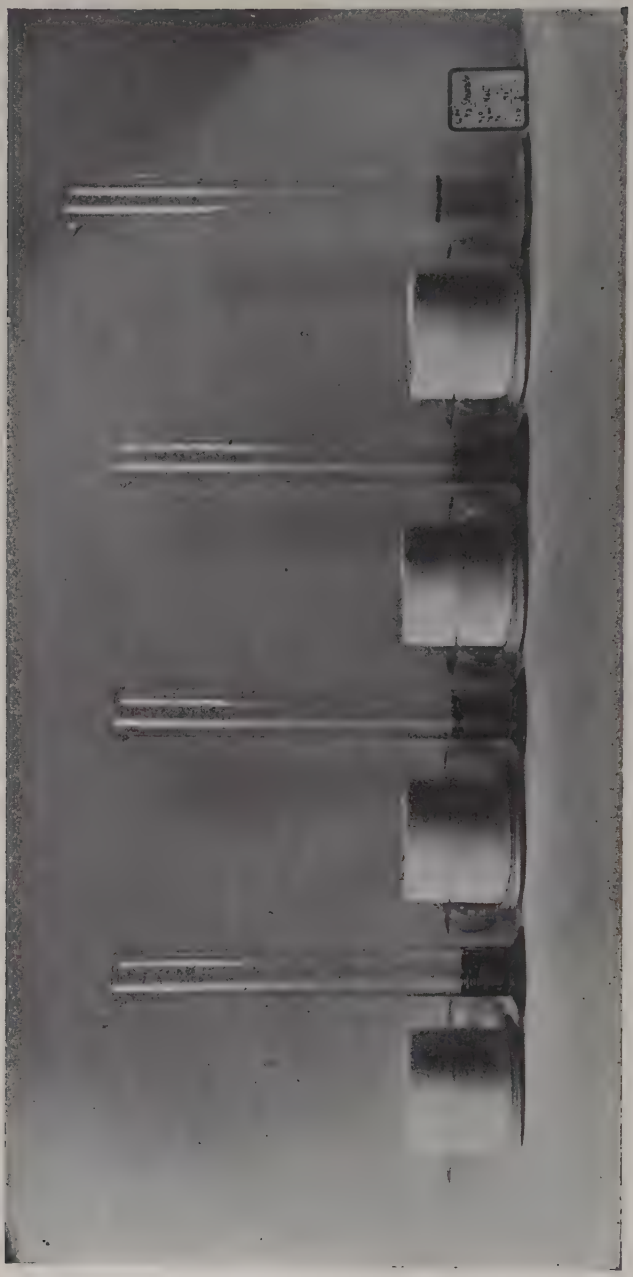


FIGURE 124.

TABLE XCIX

AMOUNT OF WATER IN CC. WHICH FILTERS THROUGH m/10 SODIUM STEARATE CUPS FROM EQUIMOLAR SOLUTIONS OF DIFFERENT SALTS

Hours allowed for filtration.	Composition of liquid being filtered.				
	H_2O	m/8 NH_4Cl	m/8 NaCl	m/8 $MgCl_2$	m/8 $CaCl_2$
:30	1	3	3	3	4
1:15	2	6	8	10	10
2:15	6	9	14	20	23
3:15	9	12	20	29	35
4:30	15	14	27	40	50
5:30	19	16	33	52	64
6:30	23	17	38	58	70
7:50	30	18	42	62	72

The results of this experiment at its end are shown in the photograph of Fig. 125.

It is to be noted that the ammonium chlorid leads to a *decrease* in secretion as compared with the effects of pure water. On the other hand, magnesium and calcium chlorid are more powerful "diuretics" than sodium chlorid. We return to a discussion of these findings later.

TABLE C

AMOUNT OF WATER IN CC. WHICH FILTERS THROUGH m/10 SODIUM STEARATE CUPS FROM EQUIMOLAR SOLUTIONS OF DIFFERENT SALTS

Hours allowed for filtration.	Composition of liquid being filtered.					
	H_2O	m/8 NaCl	m/8 Na_2SO_4	m/8 Na acetate	m/8 Na_2HPO_4	m/8 Na citrate
1	1	1	2	1	1	1
2:30	3	5	4	2	3	3
3:30	5	7	6	4	4	5
5:30	8	12	10	7	7	10
6:30	11	14	12	9	8	14
7:30	12(?)	16	13	11	9	17
24:10	37(?)	37	35	31	30	cup broken
Neutralization value in cc. n/10 H_2SO_4 of whole filtrate	.14	.7	.7	.6	.6	

We tried next the effects upon filtration of equally concentrated (*either equinormal or equimolar*) solutions of salts containing a common basic radical with different acid radicals. Table C gives

FIGURE 125.

TABLE CI

AMOUNT OF WATER IN CC. WHICH FILTERS THROUGH m/10 SODIUM STEARATE CUPS FROM EQUINORMAL SOLUTIONS OF DIFFERENT SALTS

Hours allowed for filtration.	Composition of liquid being filtered.					
	H_2O	m/8 NaCl	m/16 Na_2SO_4	m/8 Na acetate	m/24 $NaHPO_4$	m/24 Na citrate
1	1	2	2	1	1	1
2	2	4	3	1	2	2
3	4	6	4	4	2	2
4	5	7	6	4	4	4
5	6	9	7	5	5	5
6	8	11	8	7	7	7
7	9	13	9	8	7	8
22	30	32	27	28	24	28
Neutralization value in cc. n/10 H_2SO_4 of whole filtrate	1.3	.7	.8	.7	.8	.5

the results when *equimolar* solutions are used, while Table CI and Fig. 126 give the findings when *equinormal* solutions are employed. It will be observed that within the limits of experimental error there is *no change* in either case in amount of water secreted as compared with the effects of sodium chlorid. In other words, the greater diuretic action of the acetates, citrates, phosphates and sulphates observed in living animals as compared with the diuretic action of equally concentrated chlorids, bromids, or iodids does *not* appear in these filtration experiments with soaps. To the discussion of this finding we also return below.

6. There exists a variable in all the described experiments which may be made a constant when it is so desired. In the simple arrangement described above, the filtration pressure falls as the amount of liquid which passes through the cup increases. Since, besides, the filtrate is not removed as formed, more and more accumulates about the cup and thus reduces the surface available for filtration. Both objections may be overcome by utilizing the filtration arrangement with constant level shown in Fig. 127.

In Fig. 127, *b* represents in section a sodium stearate cup supported upon a coarse, galvanized iron screen held in a ring stand. In proper position above the cup is supported the inverted 100 cc. graduate *a*. At the beginning of the experiment the cup *b* and the graduate *a* are filled with the liquid to be filtered, the filled gradu-

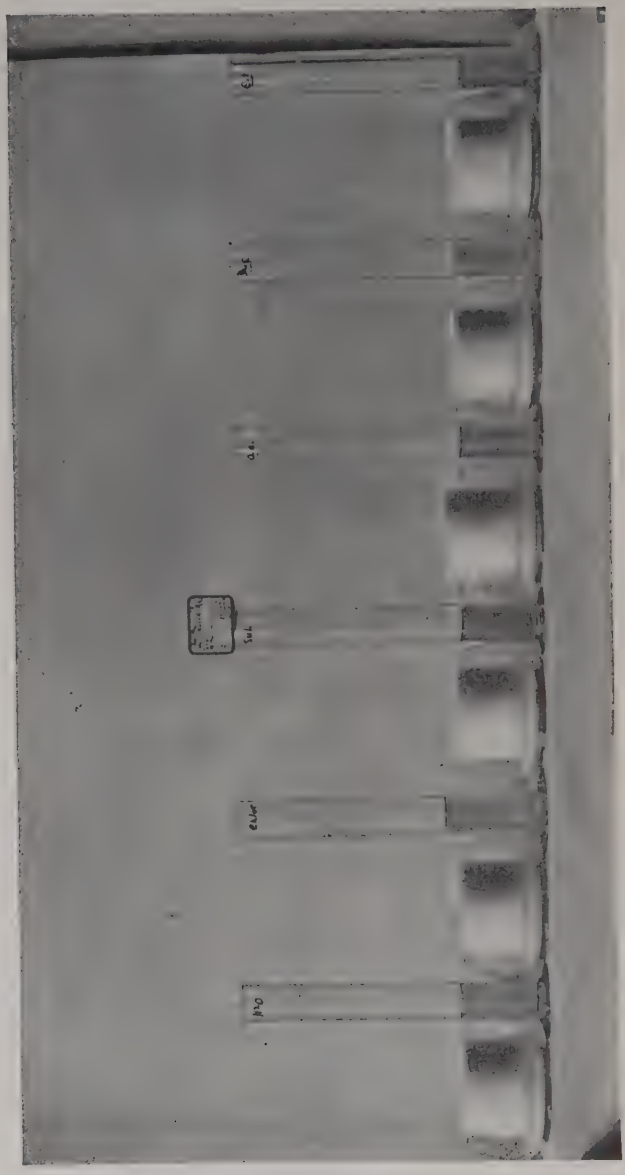


FIGURE 126.

ate being inverted and placed in position as indicated in the figure. The filtration pressure is obviously determined by the height of the liquid standing in *b*. As liquid filters through the cup and its

level falls in *b*, air enters the graduate, allowing the liquid column in *a* to fall sufficiently to restore the old level in *b*. In this way the filtration pressure available in *b* is kept constant. Any liquid which filters through *b* is caught by the funnel *c* and collected in the graduate *d* from which direct readings as to quantity of filtrate may be made.

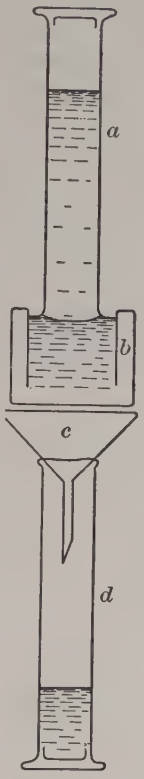


FIGURE 127.

§ 3

1. The model described above may also be used to demonstrate various facts regarding *the secretion of dissolved substances.* A first point again covers the matter of how a secretion more alkaline may be derived from a less alkaline or even neutral source (parenchyma or blood). If phenolphthalein is added to the solution being filtered, is applied to the soap of the cup, and is added to the secretion escaping from the soap cup, in such an experimental series as indicated in Table XCVIII (where water and sodium chlorid solutions of different concentrations are being filtered) the following facts may be observed. The original salt solutions leave phenolphthalein uncolored; so also do the sodium stearate cups; in the case of the filtrates, however, that from pure water turns the phenolphthalein brilliantly red. The same is true, though in decreasing intensity, as we examine the "secretions" from the cups containing increasingly stronger sodium chlorid solutions. The filtrate from the sodium chlorid of highest concentration may leave the phenolphthalein practically uncolored.

Expressed in ordinary terms, alkaline secretions are here being derived from parenchymas or blood which are by themselves neutral or even acid. There is, however, nothing mysterious in the observed facts if a previous study on the composition of the lyophilic colloids and of the behavior of the colloid soaps toward indicators is kept in mind.[1] Distilled water and aqueous solutions of neutral salts are of course not expected to color phenol-

[1] MARTIN H. FISCHER: Science, **48**, 143 (1918); ibid., **49**, 615 (1919); Chem. Engineer, **27**, 184, 271 (1919). See also page 775.

phthalein. The solid soap cups are essentially solutions of *water in sodium stearate* and such hydrated soap colloids also leave phenolphthalein uncolored. But upon diluting such a colloid, the soap dissolves in the water and such solutions of *soap in water do* color phenolphthalein. Hence the secretion which has passed *through* the solid sodium stearate is "alkaline" in reaction. This solubility of the soap in water decreases, however, as neutral salt is added to the water, hence less soap dissolves and hence less reaction to the phenolphthalein.

The biological significance of these findings (aside from the light which they throw upon the mechanism by which secretions more or less acid or alkaline may be obtained from allegedly more neutral sources) is of course great. In the terms of the pure physical chemists, the dilute soap solutions, as represented by the filtrates, are alkaline because, after hydrolysis of the dissolved soap, there is present an excess of hydroxyl ions. By the same reasoning the soap cups show no reaction to phenolphthalein because these are too "concentrated soap solutions." Even if we allow the correctness of such deductions—we are ourselves of the opinion that indicator methods are largely inapplicable here [1]—the necessary additional conclusions are still of small comfort to orthodox physiology. From a colloid point of view protoplasm behaves like the soap cup and blood and lymph like a concentrated liquid colloid of the type of sodium oleate. By the indicator methods these show no ions. Are the physical chemists who believe in the unrestricted applicability of the laws of dilute solutions to living cells going to admit that solid protoplasm and blood and lymph under normal circumstances contain practically no ions, and that they have in consequence ascribed to the theories of dilute solution, electrolytic dissociation, etc., an importance which they in no sense can exercise in normal living tissues? We believe, as a matter of fact, that normal *uninjured* protoplasm is, from a physical point of view, electrically neutral and that there are in it under normal circumstances as few or less electrically charged atoms and groups of atoms as in pure water or alcohol or ether or a dry crystal holding water of crystallization. Protoplasm is, in other words, a "solution" of water in hydrophilic colloid and this is a system to which the physico-chemical laws covering the dilute solutions

[1] Because to our minds the system *soap dissolved in water* is something totally different from the system *water dissolved in soap*. See page 52.

may not be applied without the greatest reserve. Such laws may only be applied to the solutions of protoplasm in water, as to the more watery secretions from the body like urine, saliva or sweat.

2. If, instead of testing the "secretions" in the above experiments for alkalinity, we analyze them for content of fatty acid (in other words, for amount of soap dissolved in the secretion), it is found that most soap is dissolved when plain water is filtered through the cup and less and less as salt solutions of increasing concentration are employed. This too has its biological parallel. Distilled water can not, for example, be furnished secreting cells without damaging them, for the cells tend to dissolve in such distilled water. Thus the excessive consumption of distilled water makes for the appearance of albumin in the urine. To keep a colloid parenchyma (be it soap or protoplasm) from thus going into solution, salt must be added to the distilled water. This is one of the reasons why all cells are less damaged by a so-called physiological salt solution than by plain water. In fact in the case of a kidney previously damaged by distilled water (or worse still by some powerful "solution" producing agent like an acid) the progressive solution of the kidney in the urine (the albuminuria) may be cut down by perfusion of the organ with a proper salt solution.[1]

3. We wish, finally, to return to the fact that if the rate at which distilled water filters through a soap cup is taken as the standard, the rate of such secretion from an ammonium chlorid solution is less, while that from other salt solutions like sodium, magnesium or calcium chlorid, at equivalent concentrations, is greater and in the order named. This, too, has its analog in what may be observed in animals, and the explanation of what occurs in animals may be deduced, we think, from the action of these salts upon soap. Generally speaking, all salts tend to dehydrate soaps and this in increasing amount with increasing concentration. When sodium chlorid is used there is therefore a progressive increase in dehydration of the hydrated sodium stearate constituting the soap cup and, with the secondary enlargement of the capillary pores consequent upon this, filtration is made proportionately easier. When, however, a salt capable of entering into double decomposition with the sodium stearate is used, there is added to this first effect a secondary one incident to the production of a new soap. The hydra-

[1] See page 648.

tion capacities of soaps of the commoner fatty acids with different bases runs in about the following order:

$$NH_4, K, Na, Mg, Ca.$$

(The solubility of these soaps *in* water also runs in this order.) It will now become clear, when equally concentrated solutions of these different salts are filtered through sodium stearate, why ammonium and potassium salts lead to a lesser secretion of water than sodium, and why magnesium and calcium salts lead to a greater one, and in the order named. After double decomposition and at least partial formation of the corresponding soaps, the original capillarity of the hydrated sodium stearate is changed, being decreased in the first named, left largely unchanged in the middle member, and increased in the last named.

It was emphasized above that while the "diuretic" action of equally concentrated but different salts differs when their basic radicals are different, such distinctions are largely missing when salts with a common base but different acid radicals are employed. In other words, these soap models do not show the greater diuretic action of the citrates, tartrates, phosphates and sulphates over chlorids, for example, which do animal kidneys or living cells in general. We expected this result as the necessary corollary of certain chemical differences between fatty acids and amino-acids and the possibilities possessed by the latter of forming longer series of different salts.

The action of different bases upon a fatty acid may be compared with the action of the same bases upon the polymerized amino-acid which we call protein. "Soaps" are formed in both instances with their varying hydration capacities. It is our belief, in other words, that if we write the formula for any fatty acid as:

$$x—COOH$$

that the colloid-chemical properties of the different soaps are dependent upon the substitution for the H in the above formula of the various metal radicals. If now we write the formula for an amino-acid as:

$$\begin{array}{l} x—COOH \\ | \\ NH_2 \end{array}$$

the effects of the metal radicals are again the same, and the colloid-chemical behavior of the pure proteins which are thus formed is again of the same kind as in the case of the soaps. Instead of soaps of fatty acids we get "soaps" of proteinic acid, the solvation and solution characteristics of both of which are largely the same. The fatty acids do not, however, possess the power of uniting with acid as do the amino-acids. In the latter instance acids may unite with the NH_2 groups. In this fashion there can then be produced the chlorids, bromids, sulphates, phosphates, etc., of the polymerized amino-acids each again possessed of its own solubility in water and solvent power for water. Since the cells of the living body are the hydrated salts of polymerized amino-acids, the various salts may affect them "diuretically" not only through their basic, but also through their acid radicals.

13. Concluding Remarks on Absorption and Secretion. Lymph Formation. Vasomotor and Secretory Nerves

The variable capacity of the body colloids for holding water also helps us to understand some of the phenomena of lymph formation. It seems to me that *the formatuon of lymph is in many points entirely analogous to the secretion of urine and governed by similar laws.* The "secreting membrane" in this case is found in the cells and the intercellular substances that separate the blood capillaries from the lymph capillaries.[1] It is, of course, clear that these cells and their intercellular substances constitute the bulk of the body tissues. *Anything that makes these cells with their intercellular substances yield up water increases lymph flow.*

Let us first call attention to the fact that an increased arterial circulation to a part increases lymph flow. A classic experiment in this line is the observation that an increased lymph flow from the neck is obtained when the salivary glands are active (supplied with much arterial blood). Under such circumstances various tissues in the neck are rapidly freed of their carbonic (and other) acids. This decreases the capacity of their colloids

[1] Recent histological and physiological studies indicate clearly that the lymph circulates through a series of closed tubes as does the blood. The old assumption that a direct communication existed between the two (through holes) is certainly not correct.

for water, and so they give it up, in part to the blood, in part to the lymph.

All salt solutions, when injected into the blood in sufficiently concentrated solutions, increase lymph flow. When sodium chlorid, sodium bromid, etc., are employed, these have to be injected in (osmotically) stronger solutions than when sodium sulphate, sodium phosphate, etc., are used. The same thing happens in experimental diuresis. These experiments on the formation of lymph are easily explained by saying that the salts diffuse into the tissues and make them give up their water which then passes in part into the blood, but in part again, into the lymphatics. A similar explanation can be given of the "lymphogogue" action of various sugars. Physostigmin and pilocarpin increase lymph flow; atropin and morphin decrease it. In the doses ordinarily used, the former make *in toto* for an increased supply of oxygen and the more rapid removal of carbonic acid from the cells, the latter for a decreased one. While the former means a decrease in the capacity of the tissue colloids to hold water, the latter means an increase; these in turn mean a giving up of fluid to the lymph in the first case, and none available for such a purpose in the second.

A word may not be amiss regarding the useful purpose served by *the vaso-motor mechanism* in this whole problem of absorption and secretion. Changes of both a quantitative and a qualitative character must of course follow the changes consequent upon any variation in the caliber of the blood vessels supplying a part. With blood of a given composition, it is evident that with vaso-dilatation more will flow through a part, and so the opportunities for absorption or secretion, whether of water or dissolved substances, be increased. But such quantitative changes in the blood flow through a part affect at the same time the chemical and physico-chemical character of the cells in that part, and so a series of qualitative changes in the character of the absorption or the secretion may be added to the quantitative ones already noted. It is these facts that we have to bear in mind when we attempt the analysis of the various phenomena that characterize absorption and secretion as observed, for example, in a mammal.

The organs that are predominantly secreting organs (kidney, salivary glands, stomach, pancreas) are all supplied with

large arteries, and when these glands are active, their arteries are dilated. The supply of highly arterilized blood which makes possible the secretion of gastric juice (as it makes possible the secretion of urine) makes it impossible at the same time for this organ to act as an absorptive organ. And experimentally we know the stomach to act indifferently well in this direction as far as water absorption is concerned. Other substances can, of course, be absorbed from the stomach (alcohol, salts) and be secreted into it (various salts) independently of any absorption of water. Failure to absorb water only means, of course, that the stomach wall, and the (arterial) blood coursing through it is saturated with water—the three phases of the system are in equilibrium so far as their water content is concerned. In so far as any dissolved substance is not distributed in such a way through the three systems as to be in equilibrium, it must move (be absorbed) into the stomach wall and the blood, or out of these (be secreted) into the gastric contents until the equilibrium is established. When the rich supply of arterial blood to a secreting organ fails, no secretion occurs, as can be seen particularly well in the kidneys, the salivary glands, etc., when their blood supply is cut down either through experimental constriction of the arteries supplying them, or when the vaso-constrictor nerves are stimulated.

It is true that under certain conditions no secretion may occur from a gland even when an abundant arterial flow is furnished the secreting cells, but this is only possible if the normal chemistry of the cells constituting the secreting membrane is first disturbed, as after poisoning with atropin, which so interferes with the oxidation chemistry of the cells that they are put in a state of lack of oxygen in spite of all that is flowing by them.

We can also understand the meaning of some of the morphological changes observed in the cells of any secreting organ so situated as to have alternate periods of rest and activity. While the process differs somewhat in different cells, it may be stated in general that the cells become larger during rest, and smaller during activity. The interpretation of this simple fact as generally given is very complicated. Need we say more than that they absorb water (become œdematous) when arterial blood is scarce and they cannot get rid of their carbonic acid easily; and that they secrete water, that is, shrink, when the carbonic and

other acids that are produced in cells when oxygen is scarce, are removed through a better arterial blood supply? With the swelling of the cells during a period of rest there is an accumulation of granules in the cells. Most extravagant interpretations have been made of their physiological significance. Need they be anything more than protein (including mucin) precipitates occurring in the bodies of the cells because in the period of glandular rest the reaction of the cell protoplasm tends to move toward the acid side? When the granules disappear during glandular activity it simply means a reversal of the process—they go back into solution as the reaction moves back toward the neutral point or the alkaline side. The changes observed during rest and activity of the salivary glands, pancreas, etc., therefore become similar to the changes of "cloudy swelling,"[1] observed in the liver or kidney in various pathological states (including interferences with the arterial blood supply to the cells making up these organs).

Need we also to continue our belief in "secretory" nerves? I think not. We do not know a single secretory nerve effect in the complex organism which is not preceded by a vasomotor (vasodilatation) effect, and the increased secretion is easily explained through the increased oxygen supply furnished the gland by this means. *The secretory nerves are, in other words, identical with the vasomotor nerves.* There may be vasodilatation without secretion as when defectively oxygenated blood is furnished, or the gland cells themselves are rendered incapable of using the proffered oxygen, but there is no secretion without a large arterial blood supply which is furnished some glands constantly while it is furnished others temporarily through vasodilatation.

After what has been said it is evident that no great differences exist between the essential nature of absorption and of secretion. *Secretion is only the mirror of absorption.* This truth seems simple enough, and yet it cannot be said that it has received any special attention from the workers in experimental medicine or physiology. And yet it ought to, for absorption and secretion in a complex animal bear a reciprocal relation to each other. It

[1] For a discussion of the nature and cause of cloudy swelling, see page 540, or Martin H. Fischer: Kolloid-Zeitschr., 8, 159 (1911); ibid., 8, 201 (1911).

is because this fact has been ignored that much of our present-day confusion exists in this field.

An adult organism in order to continue alive has to maintain a certain constancy of physico-chemical composition. It follows that if it absorbs anything it must secrete this again within a reasonable time thereafter. It is in this "reasonable time" and the conditions that are at the bottom of the fact that this "reasonable time" has to intervene between the absorption and the secretion of any substance that makes us lose the connection between the two, even when we deal with the absorption and secretion of substances (water, certain salts) which are not chemically changed in the body. When these facts are borne in mind, the surprise expressed by some authors that atropin or morphin, which decrease various secretions, do not similarly decrease absorption from the gut or the peritoneal cavity disappears. Hardly! These substances favor the formation and accumulation of acids in the tissues of the body, wherefore, no secretion. We should, rather, discover an *increased absorption* of water after use of these drugs, which, in fact, we do. Other anesthetics act like morphin, and other drugs like atropin. When we use such agents in our experiments we have to remember what they do, and not ignore them when we come to interpret our findings. Operations, animal boards and physiological apparatus produce collectively effects similar to drugs, so these too must not be ignored. It is for this reason, as I stated above, that all these procedures must be reduced to a minimum if we would complete our analysis of just what constitutes the physiology and the pathology of absorption and secretion.

The analysis of the problems of absorption and secretion could already be carried with entire safety beyond the limits outlined here and in my previous papers, which have had as their chief aim the mere establishment of the thesis that the colloids and their physical state determine both the quantitative and the qualitative character of the absorption and secretion of water and dissolved substances by protoplasm. This will be done elsewhere.[1] In passing, however, attention must be called to the excellent service that will be rendered the further analysis of the problem by the theories of the colloid state which

[1] See pages 52, 59, 396, 527 and 775 and MARTIN H. FISHER: Soaps and Proteins, New York (1920), *in press*.

are becoming progressively more clearly defined. Especially helpful to the biological worker must become the conclusions of WOLFGANG PAULI[1] and his co-workers,[2] more particularly HANS HANDOVSKY[3] and KARL SCHORR,[4] as well as those of R. C. TOLMAN,[5] whose theoretical deductions regarding the colloid state seem broader and less capable of adverse critical attack than any yet proposed.

The theoretical elucidation of the absorption and secretion of *dissolved substances* will necessitate adequate use of WOLFGANG OSTWALD'S[6] work. OSTWALD has shown that the mathematical formulas of adsorption are applicable to the process of absorption (intoxication) as shown in certain fresh-water animals (*Gammarus*) when they are placed in solutions of various kinds. It is evident that these animals swimming about in a solution are no differently situated than a group of cells, say, in the mucous membrane of the intestine, which are bathed by such a solution. But OSTWALD has developed the biological significance of what represents in a sense the mirror image of the adsorption formula, namely, the washing-out formula. This may be used to express mathematically the "toxic effect" of distilled water upon these animals—an effect brought about by the diffusion out into the distilled water of the salts contained in the animal. It is evident that the leaching out of dissolved substances from the kidney by the pure water originally secreted from the organ constitutes the parallel of this "toxic effect" of the distilled water on *Gammarus*. OSTWALD has further shown that the effect of a solution having but one salt dissolved in it is the composite of the adsorption effect of that salt plus the washing out effect of all the other salts contained in the animal but absent from the solution that is being experimentally employed. This phenomenon has its analogue in the experimental absorption of any pure solution from the intestinal tract

[1] WOLFGANG PAULI: Kolloid-Zeitschr., **7**, 213 (1910).

[2] WOLFGANG PAULI and HANS HANDOVSKY: Biochem. Zeitschr., **18**, 340 (1909).

[3] HANS HANDOVSKY: Kolloid-Zeitschr., **1**, 183 and 267 (1910), where references to earlier papers will be found.

[4] KARL SCHORR: (Cited by PAULI and HANDOVSKY).

[5] R. C. TOLMAN: Jour. Am. Chem. Soc., **35**, 307 (1913); **35**, 317 (1913); Science, **44**, 565 (1916).

[6] WOLFGANG OSTWALD: Pflüger's Arch., **120**, 19 (1907); Kolloid-Zeitschr., **2**, 108 and 138 (1907). WOLFGANG OSTWALD and A. DERNOSCHEK: Kolloid-Zeitschr., **6** (1910).

of a mammal, for example, in which, as was noted above, there is a "secretion" of dissolved substances from the intestinal wall into the gut, while the dissolved substance originally introduced is being "absorbed."

IV

MAINTENANCE OF THE CIRCULATING FLUIDS IN THE BODY

1. Why the Blood Remains in the Blood Vessels

We have up to this point been chiefly interested in the mechanism by which we manage to get a secretion from the blood, and by way of illustration have discussed with particular intensity the mechanism by which more or less water may be obtained from a kidney. We have seen how a kidney will secrete only as water is brought to it, and this in proportion to the amount of "free" water furnished. Let us now change our viewpoint, and instead of asking how we may get more urine from the blood, ask why all the blood is not poured out as urine (or some other secretion), in other words, *why does the blood remain in the blood vessels?* [1] This is biologically just as important, and medically and surgically just as practical a question as that of the ways and means by which a urinary secretion is maintained and increased or decreased.

The maintenance of a normal circulation is absolutely necessary in the complex organism. It provides the individual cells with the materials necessary for their life, while at the same time it carries away the poisonous substances produced by them, which, if allowed to accumulate, threaten their existence. What is said in these paragraphs holds for both the blood and the lymph, but unless otherwise stated, we shall limit ourselves to the problem of the circulation of the *blood*. For the maintenance of a circulation we need a properly working pump and a suitable *circulating fluid*.

The question of what constitutes a suitable circulating fluid may be discussed from two points of view, from a chemical and

[1] See MARTIN H. FISCHER: "Œdema," 186, New York (1910); Kolloidchem. Beihefte, **2**, 324 (1911); JAMES J. HOGAN and MARTIN H. FISCHER: Kolloidchem. Beihefte, **3**, 385 (1912).

from a physical. The chemical side will be touched upon but incidentally. Our chief interest lies in certain physical aspects of the problem.

Since our experimental studies were instigated by consideration of some problems in practical medicine, our discussion may begin with these. That part of the problem of maintaining a normal circulation which has to do with the existence of a suitable circulating fluid is usually taken pretty much for granted. We shall see later that this is dangerous. The coarser disturbances which may affect a circulating fluid like the blood are, however, familiar to every clinician and are striking enough. We need but call to mind the consequences of hemorrhage. If by accident or otherwise one of the larger vessels is opened in man or a laboratory animal, we see following each other in the course of a very few minutes all those alarming symptoms which culminate in death.

When now we try to say why this occurs it is quickly brought home to us that the most serious mischief done by the hemorrhage does not reside in a great loss of red blood corpuscles or in a loss of certain of the chemical constituents found in the blood, say the hemoglobin or certain salts, but in a diminution in the volume of the circulating blood. The proof for such a conclusion is easily brought, for to protect or save an animal from the effects of hemorrhage it is not necessary to transfuse blood; but transfusion with water containing various salts (so-called "physiological salt solution," "RINGER solution" or "LOCKE solution") may do. In fact, the dangers incident to transfusion of whole blood have made medical men in practice depend more and more upon salt solutions of various kinds and less upon the transfusion of blood itself.

But even though salt solutions of various kinds work excellently, they do this only for a limited time. In other words, it is too often noted that while a physiological salt solution or a RINGER solution produces immediately brilliant results, this effect wears off in an hour or two so that the individual who has been roused from the threatening effects of a great hemorrhage begins to sink again, and even though we repeat our injection, the improvement in patient or animal is again only temporary.

It is easy to see why this happens. *The injected salt solution does not remain in the blood vessels.* Proof of this is at hand.

Not only does the blood pressure attained after the injection gradually fall, but the injected fluid leaves the body as urine or is taken up by the tissues (an œdema develops) or both. If the water could be retained in the blood vessels we should get more lasting results from the injection of a salt solution. We are now in the heart of the problem and theme of these paragraphs. As seen in the experiments on the intravenous injection of blood and blood serum already described above,[1] *the blood remains in the blood vessels* (*and the lymph in the lymph vessels*) *because the water is all held as hydration water combined with the colloids of the blood* (*and lymph*), *and in this form cannot escape as a secretion.*

To meet the objection that the blood remains in the blood vessels because of some specific property and not simply because all its water is held in combination with the colloids of the blood, we insert Fig. 128 and Experiments 47 and 48 where water is again injected intravenously, but this time in combination with a colloid foreign to the blood, namely, gelatin.

Experiment 47, which describes the intravenous injection of a pure 2 per cent gelatin solution, is inserted merely for purposes of control. Such a solution yields no rise in urinary output (see Curve *b* of Fig. 128), but objections may be raised to this experiment. As the protocol shows, the animal develops hemoglobinuria and albuminuria, casts appear in the urine and the urinary secretion is very low, in other words, it develops a "nephritis." It could justly be charged, therefore, that such an animal secretes no water simply because it is nephritic. One of the causes of this nephritis resides in the acid properties of the gelatin used, but the whole picture cannot be thus explained. The pure gelatin solution produces all the signs and symptoms following injection of an equal amount of distilled water. The injection of this causes no rise in urinary output, but only because the destructive action of the water on the blood with its consequent interference with the normal oxidation chemistry

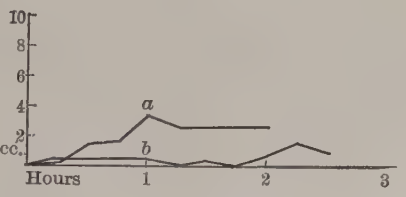


FIGURE 128.

[1] See page 336

of the body more than offsets the diuretic action of the water alone.

There are therefore at least two factors responsible for the poisonous effects of a pure gelatin solution, its acid content and the retention in its hydration water of those properties of distilled water destructive to the blood. This conclusion is of importance not only from the standpoint of practical medicine, but also from that of the theory of the colloid state.

We can avoid the practical and theoretical objections to the experiment just described by adding a salt to the gelatin solution as in Experiment 48. Then there is no hemolysis, no hemoglobinuria, no albuminuria, no casts, and the urinary output is normal (see Curve *a* in Fig. 128). This experiment proves that water in combination with a colloid (gelatin) remains in the blood vessels.[1]

Experiment 47. *Injection Fluid:* 2 per cent gelatin solution. Belgian male rabbit. Weight 1448 grams. Kept on standard mixed diet.

72.4 cc. of the above solution, an amount estimated as equivalent to the total blood volume of the animal, are injected into an ear vein at the uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
2.15	.....	Tied down, catheterized, injection begun.
	7.0	Clear, yellow, no albumin.
2.30	0.5	Clear, yellow.
2.45	0.4	Slightly bloody, albumin.
2.55	.....	Injection ended.
3.00	0.4	Somewhat bloody.
3.15	0.4	Bloody, many yellowish casts.
3.30		
3.45	0.2	Same.
4.00	One drop	The color of port wine, many yellow casts.
4.15	0.5	Same.
4.30	1.4	Same.
4.45	0.8	Same.

Animal released.

Total urine in two and one-half-hour period since beginning of injection, 4.6 cc.

Animal found dead in cage next morning.

[1] H. Roger and Garnier (Soc. de Biol., Mai 4 (1912); Compt. Rend. Soc. de Biol., Mai 5 (1912)) have also found an increased urinary output after intravenous injection of Locke's solution, but none when gelatin was added to this. They conclude that solutions "isoviscid" with the blood do not act diuretically but attempt no explanation of the fact.

Autopsy: Peritoneal and pleural cavities contain a little bloody fluid.
Heart is filled with blood.
Kidneys, grayish and swollen.

EXPERIMENT 48. *Injection Fluid:* 2 per cent gelatin in m/8 NaCl. White male rabbit. Weight 1249 grams. Kept on standard mixed diet.

62.5 cc. of the above solution, an amount equivalent to the total blood volume of the animal, are injected into an ear vein at the uniform rate of 10 cc. every five minutes. No anesthetic.

Time.	Urine in cc.	Remarks.
10.45	.....	Tied down, catheterized, injection begun.
	0.2	Cloudy, yellow, alkaline, no albumin.
11.00	0.2	Same.
11.15	1.5	Cloudy, yellow, alkaline, no albumin, no blood. Injection ended.
11.30	1.7	Same.
11.45	3.2	Same.
12.00	9.6	Same.
12.15	2.5	Same.
12.30	2.5	Same.
12.45	2.5	Clear, no albumin, no blood.
1.00	2.5	Same.

Animal released in good condition.

Total urine in the two and one-quarter-hour period since beginning of injection, **19** cc.

If the explanation of the foregoing protocols is correct we should be able so to arrange our experiments that water will be retained in the blood vessels of an animal or secreted, depending upon whether we introduce it in combination with a colloid or as "free" water. Such proof must, moreover, be adducible in one and the same animal. Fig. 129 shows the results when the injection of horse serum (water in combination with a colloid) is followed by one of salt solution ("free" water). Curves *a*, *b*, and *c* correspond to Experiments 49, 50, and 51, respectively. It is strikingly apparent that as long as we inject blood serum there is no increase in urinary output, whereas it rises enormously as soon as the salt solution is started.

EXPERIMENT 49. *Injection Fluids:* Horse-blood serum followed by m/2 (2.9%) NaCl. White rabbit. Weight 1417 grams. Kept on standard mixed diet.

90 cc. of the serum, an amount equivalent to about $1\frac{1}{3}$ times the total blood volume of the animal, are injected into an ear vein at the uni-

form rate of 10 cc. every five minutes. 60 cc. m/2 NaCl solution are then injected in the same way.

Time.	Urine in cc.	Remarks.
10.00	.....	Tied down, catheterized, injection begun.
	0.3	Clear, dark amber, no albumin.
10.15	0.3	No albumin.
10.30	7.5	Neutral, faint trace of albumin.
10.45	5.0	Clear, neutral, albumin, one cast.
		Injection of serum ended and injection of NaCl solution begun.
11.00	18.0	Last part clear as water, faint trace of albumin, one cast.
11.15	78.0	Clear as water, neutral to litmus, faint trace of albumin.
		Injection of NaCl solution ended.

Animal released in good condition; eats and drinks at once.

Next morning the animal is alive and well.

Total urine in the forty-five-minute period of the serum injection, **12.8** cc.

In the next forty-five-minute period of the salt injection, **134.0** cc.

Experiment 50. *Injection Fluids:* Horse-blood serum, followed by m/2 (2.9%) NaCl. Black male rabbit. Weight 1795 grams. Kept on standard mixed diet.

90 cc. of the serum, an amount equivalent to the total blood volume of the animal, are injected into an ear vein at the uniform rate of 10 cc. every five minutes. 90 cc. of the NaCl solution are then injected in the same way.

Time.	Urine in cc.	Remarks.
11.00	.....	Tied down, catheterized, injection begun.
	0.5	Clear amber, alkaline, no albumin.
11.30	1.8	Same.
11.45	3.8	Clear amber, alkaline, faint trace of albumin, three casts.
		Injection of serum ended and injection of NaCl begun.
12.00	32.0	Last part clear as water, alkaline, faint trace of albumin, no casts, no red blood corpuscles.
12.15	67.5	Clear as water, neutral, no albumin.
12.30	75.0	Same.
		Injection of NaCl ended.
12.45	22.5	Same.
1.00	8.0	Same.

Animal released in good condition.

Next morning is alive and well.

Total urine in the forty-five-minute period of the serum injection, **5.5** cc.

In the forty-five-minute period of the salt injection, **174.5** cc.

EXPERIMENT 51. *Injection Fluids:* Horse-blood serum, followed by m/2 (2.9%) NaCl. Mixed Himalaya rabbit. Weight 1593 grams. Kept on standard mixed diet.

25 grams of blood are taken from the carotid artery, an amount equivalent to about one-third of the total blood volume of the animal.

96 cc. of serum are then injected at the uniform rate of 10 cc. every five minutes into an ear vein. This amount is about $1\frac{1}{6}$ times the blood volume of the animal.

60 cc. of the NaCl solution are then injected in the same way.

Time.	Urine in cc.	Remarks.
1.35	.....	Tied down. Drawing of the 25 grams of blood from the carotid artery begun.
1.55	0.3	Bleeding ended and injection of serum begun. 36 cc. are injected in the first five minutes, then at the uniform rate of 10 cc. every five minutes.
2.10	2.3	Clearing, trace of albumin.
2.25	3.0	Slightly red, albumin, no casts, no red blood corpuscles.
2.30	.....	Injection of serum ended and injection of NaCl begun.
2.40	7.5	Last part clear, faint trace of albumin.
2.55	61.0	Clear, trace of albumin.
3.00	.....	Injection of NaCl ended.
3.10	6.30	Same.

Animal released; found dead in cage next morning.

Total urine in the thirty-five-minute period of the serum injection, 5.3.

In the following forty-minute period of the salt injection, **131.5** cc.

In Experiments 49, 50, and 51 the injection of horse serum was followed by an albuminuria. This albuminuria is attributable to the large injections made, in consequence of which the circulatory system becomes overfilled. This leads to circulatory disturbances which affect the kidneys (and other organs) resulting in the appearance of casts and albumin in the urine. The dyspnea caused by such large injections of serum is plain evidence of the general disturbance. Interestingly enough it can be made to disappear in a few minutes by injecting a strong salt solution, for this dehydrates the blood colloids and as the freed water escapes through the kidneys the volume of fluid in the blood vessels sinks nearer the normal.[1]

[1] C. H. NEILSON: Jour. Am. Med. Assoc., **40**, 436 (1913), has made a careful study of the effects of various salines on the high blood pressure shown by different types of patients. The salines decrease the blood pressure. It is an interesting fact that they do this in the order in which they dehydrate colloids. The salines dehydrate the liquid blood, of course, as they do the rest of the body and as the volume of circulating fluid in proportion to the capacity of the blood vessels for holding it falls, the blood pressure must sink.

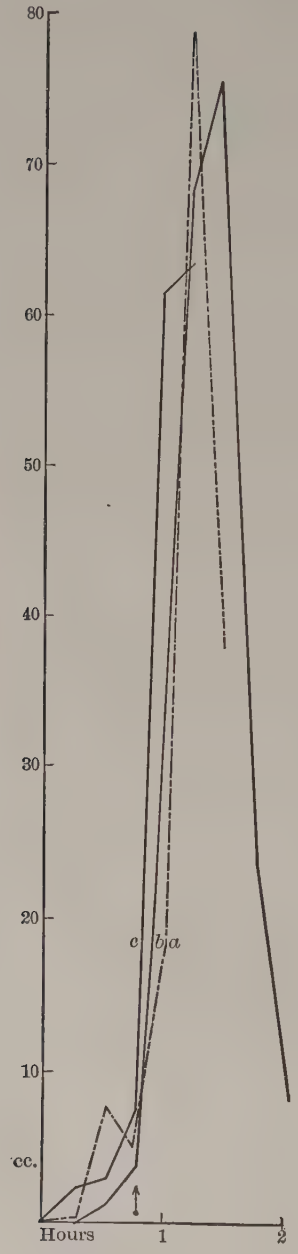


FIGURE 129.

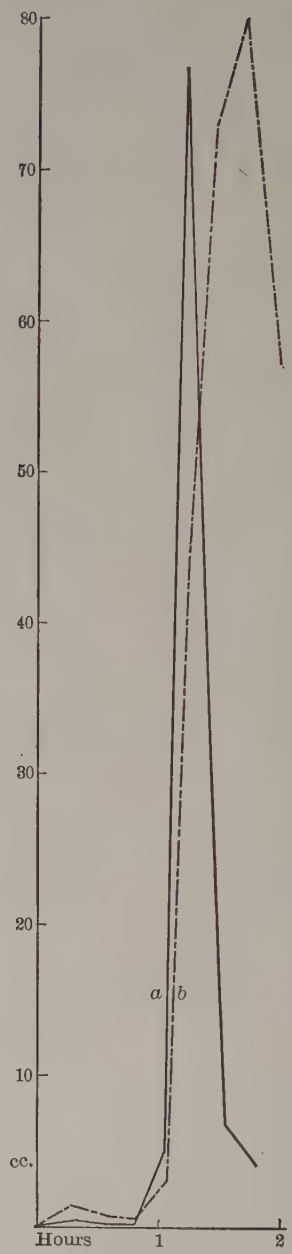


FIGURE 130.

Curves *a* and *b* of Fig. 130 are based on Experiments 52 and 53; they show results similar to those of Fig. 129, except that in these experiments the water was held in combination with gelatin instead of the colloids of blood. In Experiment 52 we used a pure gelatin solution, in Experiment 53 a gelatin solution in a weak salt solution. What we said above regarding the relative toxicity of such solutions is true here, and the analogous effects on the animal show plainly in the protocols.

In Experiment 54 the water was held in combination with the colloid casein. The casein solution was prepared by neutralizing the ordinary (acid) casein prepared by HAMMARSTEN'S method with a weak sodium hydroxid solution and adding enough sodium chlorid to bring the final mixture to the concentration of a "physiological" (0.7 per cent) solution. The effects of a casein solution without the sodium chlorid are the same as those of a pure gelatin solution. Fig. 131 based on this experiment needs no explanation.

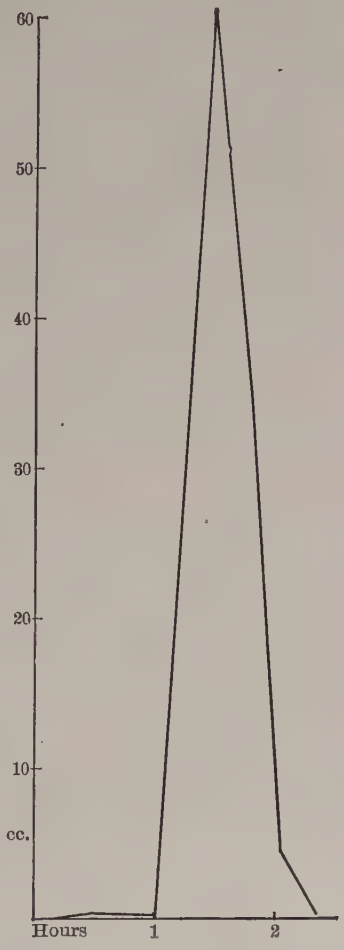


FIGURE 131.

EXPERIMENT 52. *Injection Fluids:* 2 per cent gelatin solution followed by m/2 (2.9%) NaCl. Belgian male rabbit. Weight 1822 grams. Kept on standard mixed diet.

91 cc. of the gelatin solution, an amount equivalent to the total blood volume of the animal, are injected into an ear vein at the uniform rate of 10 cc. every five minutes.

91 cc. of the NaCl solution are then injected in the same way.

Time.	Urine in cc.	Remarks.
9.50	.....	Tied down, catheterized.
	2.8	Yellow, alkaline, no albumin.
10.15	0.4	Injection of gelatin solution begun.
10.30	0.6	Cloudy, yellow, alkaline, no albumin.
10.45	0.3	Same.
11.00	0.3	Same. Injection of gelatin solution ended, injection of NaCl solution begun.
11.15	5.0	Bloody, alkaline, albumin, filled with long, coarse-grained casts.
11.30	76.0	Pale red, faintly alkaline, trace of albumin, no casts. (hemoglobinuria).
11.45	6.9	Same. (Rapid breathing.) Injection of NaCl ended.
12.00	4.3	Hemoglobinuria.
12.15	.....	Animal released, breathing short and rapid, head held high.
2.45	.....	Animal dies.

Autopsy.—In peritoneal and pleural cavities some bloody fluid containing no red blood corpuscles.

Total urine in forty-five minute period of gelatin injection, **1.2** cc.

In the forty-five minute period of the salt solution injection, **87.9** cc.

Experiment 53. *Injection Fluids:* 2 per cent gelatin solution in m/8 NaCl, followed by m/2 NaCl solution. Yellow male rabbit. Weight 2083 grams. Kept on standard mixed diet.

104 cc. of the gelatin solution, an amount equivalent to the total blood volume of the animal, are injected into ear vein at uniform rate 10 cc. every five minutes.

104 cc. of the NaCl solution are then injected in the same way.

Time.	Urine in cc.	Remarks.
11.00	.....	Tied down, catheterized, injection begun.
	2.3	Dark amber, alkaline, no albumin.
11.15	1.5	Same.
11.30	0.8	Dark amber, alkaline, faint trace of albumin.
11.45	0.4	Same.
11.50	.....	Injection of gelatin ended.
12.00	3.0	Clearing, alkaline, faint trace of albumin, no casts, no blood. Injection of NaCl begun.
12.15	44.0	Clear as water, faintly alkaline, no albumin.
12.30	72.0	Same. Injection of NaCl ended.
1.00	56.5	Same.

Animal released in good condition.

Next morning alive and well.

Total urine in forty-five minute period of gelatin injection, **2.9** cc.

In the forty-five minute period of the salt solution injection, **172.5** cc.

EXPERIMENT 54. *Injection Fluids:* Casein solution made by dissolving 8 grams casein and 1.4 grams NaCl in 200 cc. n/30 NaOH followed by m/2 (2.9%) NaCl. Belgian male rabbit. Weight 2098 grams. Kept on standard mixed diet. No anesthetic.

104.9 grams of the casein solution are first injected into an ear vein at the uniform rate of 10 cc. every five minutes. This is followed by 104.9 cc. of the NaCl solution injected in the same way.

Time.	Urine in cc.	Remarks.
2.15	.....	Tied down, catheterized, injection begun.
	0.4	Amber, acid, no albumin.
2.30	——	
2.45	0.2	Acid, no albumin.
3.00	0.2	Amber, acid.
		On addition of acetic acid a white precipitate is thrown down which disappears on the addition of more acetic acid. If this precipitate is filtered off, the filtrate gives no albumin reaction on the addition of concentrated nitric acid. The acetic acid precipitate disappears on heating, but on cooling is again formed.
		No casts, no red blood corpuscles.
3.05	.....	Injection of casein solution ended.
3.15	One drop	Injection of NaCl begun.
3.30	36.0	Last part clear as water, faintly acid.
		Albumin reaction as at 3 o'clock.
3.45	60.0	Clear as water, neutral.
		Albumin reaction as described.
4.00	35.0	Same.
4.15	4.4	Same.
4.30	0.2	Same.
5.00	.....	Animal released and returned to cage.
5.30	.....	Animal dies.

Mere inspection of the animals during the injection of a colloid solution or a salt solution shows that in the first case the injected fluid is retained in the blood vessels, while in the second it is not. If we palpate the superficial blood vessels (veins and arteries of the skin and ear, the carotid and femoral arteries) we note that during the injection of a hydrophilic colloid solution they become gradually fuller and remain so. As the blood vessels become more distended the amplitude of the pulse lessens, and this effect persists. Even when the non-poisonous blood serum is injected the animal's breathing becomes disturbed before long, and if the injection is continued the animal dies from mere overdistention of its blood vessels with its resulting mechanical disturbances in the circulation of the blood.

The injection of a salt solution is not attended by such consequences. The distention of the blood vessels is not so marked and the effect is not lasting. There is no disturbance in breathing and if a dyspnea was previously induced by distention of

the blood vessels with a colloid solution it improves. Or if we have first brought on a (presumably) fatal hemorrhage and then saved the animal by an injection of serum, we may kill it subsequently by injecting a concentrated salt solution (which again diminishes the volume of the blood in the blood vessels, as in Experiment 51).

Autopsy of the animal also shows that only the colloid solution remains in the blood vessels. When an animal has been injected with salt solution (especially if concentrated) the amount of blood in the heart and large blood vessels is normal or even below normal. On cutting through organs like the liver or kidney they bleed but little, or are quite dry. But if we have injected a colloid solution, the heart and large vessels are filled with blood and on cutting through one of the parenchymatous organs it wells out.

Still other facts show that the colloid solution remains in the blood vessels. It simply cannot get out. Its escape from the blood vessels, which represent a closed system of tubes, is analogous to its disappearance from the serous cavities or the gastro-intestinal tract. Water bound to a colloid (blood, lymph, gelatin solution, agar-agar, native albumin) cannot be absorbed as such by the peritoneum, or the mucosa of the gastro-intestinal tract, as previously emphasized, and the same holds for the blood in the blood vessels and the lymph in the lymph vessels.

Finally—and to many physiologists and clinicians this will seem most convincing—direct measurements of blood pressure show that colloid solutions remain in the blood vessels while salt solutions do not. The rise in blood pressure after the injection of a 0.9 per cent sodium chlorid solution into a non-anesthetized rabbit is only temporary—in from five to thirty minutes the pressure sinks once more to its normal level. At the same time the urinary output rises. The same is true in patients. The intravenous injection of two or three liters of properly prepared salt solution does not change the blood pressure at all. If the same amount of water is injected in the form of blood serum, or a gelatin solution, the blood pressure rises from 10 to 25 mm. of mercury and remains there. At the same time there occurs no increase in urinary output. Such findings are especially marked in the abnormally low blood pressures following hemorrhage. While salt solutions effect perhaps a tem-

porary rise in pressure (and for the time being a general improvement in the symptoms consequent upon the hemorrhage) a permanent rise results from an injection of blood serum.

2. On the Treatment of Shock

The foregoing experiments were made in order to formulate more clearly the principles that must govern us in the treatment of those various pathological conditions that are characterized by an abnormally low blood pressure. A low blood pressure may have many causes; if it becomes especially low it is fatal to both man and beast. Why in a given condition the blood pressure is low is answered in very different ways by different authors. But on the question of therapy all authors agree that the maintenance of life becomes possible only if we succeed in raising the blood pressure and keeping it raised until the patient has overcome the condition that led to the low blood pressure.

Such a low blood pressure may result from any one or any combination of the following causes:

1. A decrease in the force or number of the heart beats.
2. A diminution in the volume of the circulating blood.
3. An increase in the capacity of the blood vessels to hold fluid.

Or to illustrate this in ordinary clinical terms, a low blood pressure may result from a weakened heart muscle (myocarditis); from a hemorrhage, or a loss of the watery constituents of the circulating blood (oligemia); from a vasodilatation due either to a loss of tone in the blood vessel walls themselves or to impairment of the nervous (so-called vasomotor exhaustion) or chemical mechanisms (loss of the active principle of the suprarenal bodies from the blood) which are in part or wholly responsible for the maintenance of this tone.

In these paragraphs we shall disregard the question of failure of the heart itself as responsible for a pathologically low blood pressure and discuss merely the principles involved in our ordinary therapeutic attempts at restoring a low blood pressure to normal by introducing fluids intravenously.

The simplest problem of low pressure is presented by the ordinary cases of severe hemorrhage. We have learned why injection of a "physiological" salt solution into such patients

is so often disappointing. *Only by injecting a suitable colloid solution can we expect to bring up the pressure and have it stay up, for only such remains in the blood vessels.* What kind of a colloid solution can we use and which is best fitted for the purpose?

After what has been said it is self-evident that the best transfusion fluid is whole blood. But the obvious difficulties and dangers attendant upon the carrying out of a man to man blood transfusion limits its usefulness. The liquid of next choice for perfusion is that which most nearly approaches blood, namely, blood serum. Human blood serum is, however, difficult to obtain. The possibility of getting a human colloid solution that will stay in the blood vessels resides in the use of hydrocele fluid and of the ascitic accumulations from cases of heart disease. Such fluids can be drawn when opportunity offers into sterile containers and the serum separated from the fibrin clot by the methods employed in collecting horse serum. The use of the serum from human milk is also to be counted in here. Certain dangers are, of course, attendant upon the use of any of this human material, but upon these not overly much emphasis is to be laid, for perfusion is not at present employed in cases that are not desperately ill.

It would be ideal if we could obtain a pure colloid solution for intravenous injection from other than human sources. But the number of available substances is very small and their use always connected with some danger. The only blood derivative seems to be horse serum. The danger incident to the intravenous injection of even large amounts of this appears small in comparison with the certainty of death in cases where we are inclined to resort to such transfusion.

During the past seven years JAMES J. HOGAN[1] has made good use of properly prepared gelatin solutions in cases of hemorrhagic, surgical and toxemic shock. The first to aid him by trying gelatin solutions in surgical patients in whom death seemed the only prospect was B. F. ALDEN.

Gelatin solutions intended for intravenous use must be prepared only from the purest gelatin. The ordinary gelatins are likely to contain much acid and the products of protein decomposition, which when injected intravenously are highly poisonous.

[1] JAMES J. HOGAN: Personal communication (1913); see also Jour. Am. Med. Assoc., **64**, 721 (1915).

All preparations of gelatin should be tested for these substances. In any case they should be thoroughly washed, and if conveniences for so doing are available, in running, sterilized, distilled water. An amount of moist gelatin the equivalent of 25 grams of the dry material is then placed in 1000 cc. of freshly distilled water containing 10 grams of sodium chlorid and 2 grams of sodium carbonate crystals ($Na_2CO_3 \cdot 10H_2O$.) The whole is then autoclaved for an hour at 120° C. The gelatin solution must be prepared exactly as here described, otherwise trouble will be encountered from the fact that, as ordinarily done, the heating necessary to sterilize the gelatin properly decomposes it and so destroys the very properties for which it is used.

The following cases taken from JAMES J. HOGAN'S series may serve as illustrations of what has been said.

CASE I.—(DR. B. F. ALDEN, San Francisco.) A. F., a 39-year old Italian laborer, had always been in good health. On March 3, 1913, he was brought from the country into the French Hospital, the victim of a severe accident which had occurred the day before. A tree limb had fallen across his right leg, crushing the upper end of his tibia, and the head and lower third of the shaft of the femur. All structures beneath the skin, with the exception of the semitendinosis tendon, had been completely severed. There existed also a compound fracture which, however, did not bleed, as all vascular communication had been severed above. The left tibia and fibula were fractured. Hemorrhage had been excessive, as practically no attempt had been made to control it.

The patient was in a state of profound shock. He was almost exsanguinated and showed a small, rapid, soft, radial pulse with cold extremities, excessive thirst, and shallow and rapid respiration. Blood was oozing from the lacerated wound about the knee. Strychnin, normal salt solution subcutaneously, gelatin subcutaneously, and the usual hemostatic measures were all used without improving the general state of the patient. Under one-half grain tropococain anesthesia, administered intraspinally, the integument, which with a single tendon alone united the crushed leg to the patient, was severed. The clotted blood and crushed bone were removed and the large vessels in the stump rapidly ligated; the wound was dressed and the patient rushed to bed where his head was placed low and surface heat applied. The pulse could now no longer be obtained at the wrist, and as death seemed imminent it was felt that an intravenous injection of a gelatin solution was justified.

500 cc. were given. As there was no radial pulse at the beginning of the injection an accurate blood-pressure reading could not be made. The needle of a Tycos instrument oscillated at 90 mm. While the

injection was being made the radial pulse gradually returned and an hour later the blood pressure measured 125 mm. During the same time the pulse rate dropped from 130 to 88. The pressure was maintained, rising slightly from day to day, until on the tenth day after the infusion it measured 145, while at the same time the pulse gradually dropped to 78. The pressure now gradually declined to 125 mm. and the pulse to 72. The patient made an uneventful recovery.

Case II.—(Dr. D. N. Richards, San Francisco.) Mrs. E. S. R., entered St. Francis Hospital July 2, 1913, at 5.30 p.m. at full term and in labor. Regular pains contained until 4.15 a.m. when ether was given and she was delivered of a female child. The placenta was expelled at 5.10. This was followed by profuse bleeding, which continued until the patient was practically exsanguinated. At 6 a.m. the radial pulse could scarcely be felt. Her pulse was 140, her blood pressure (verified by Drs. Richards and Fraser) 58 mm. As her condition was considered alarming, an intravenous injection of 750 cc. of gelatin solution was given. The blood pressure rose to 118 mm. within an hour, her pulse fell to 100, and her general condition improved greatly. For the following four days the pressure varied between 105 and 110 mm., the pulse between 85 and 100. The patient made a good recovery, leaving the hospital July 17.

Case III.—(Dr. B. F. Alden, San Francisco.) J. P. G., a 46-year old Frenchman, was operated upon by an associate on February 7, 1913, for a ruptured appendix. A suppurative peritonitis with two fecal fistulas, one into the cecum, the other into a loop of the ileum resulted. On April 15 the openings in the gut were repaired with Connel's interrupted sutures of silk covered with continuous Lembert catgut sutures. No excessive bleeding was noticed at the time of the operation, but one of the Connel sutures must have lacerated a large vessel from which an active hemorrhage into the lumen of the gut resulted. On April 16 a lowered blood pressure with symptoms indicative of hemorrhage were observed. The outer wound was opened and the intestinal site explored, but as no serious bleeding was found the gut was not disturbed. The wound was repacked with gauze. On the morning of April 18 a large bowel movement of coagulated blood was observed. In the meantime the patient had declined, steadily. 10 cc. of horse serum were injected subcutaneously. A second blood stool containing a large amount of fresher blood occurred, when another 10 cc. of horse serum and 300 cc. of physiological salt solution were given. The patient continued to decline, exhibiting all the alarming symptoms of active hemorrhage. At 3.30 p.m. on April 18 the patient was reported dying. He was pulseless at the wrist. Oscillations in a Tycos instrument were observed at 80 mm. An immediate intravenous injection of 500 cc. of gelatin solution was ordered. Half an hour later the patient's pulse had dropped from 156 beats to 138 and had gained in volume, strength and regularity. The blood pressure rose to 110 mm. and by the following morning it was 140 mm. This pressure persisted while

the pulse rate within three days gradually fell to 74. An uninterrupted convalescence followed and at the present time this patient is well.

Case IV.—(Drs. W. B. Coffey and C. A. Walker, San Francisco.) Mr. B. entered St. Francis Hospital July 26, 1913, having been ill for four days. The patient showed marked evidences of general intoxication. Examination revealed tenderness in the region of the appendix. An immediate operation was performed which revealed a ruptured appendix with marked, circumscribed peritonitis. The patient showed great shock after the operation. A 0.9 per cent sodium chlorid solution was dripped into the rectum throughout the day following the operation. The patient did not rally. His pulse became progressively weaker and rose to 130, while his blood pressure fell, until at 9.30 p.m. it measured 86 mm. As death seemed the only outcome, gelatin solution was given intravenously. This was started at 9.50, the blood pressure at this time measuring 85 mm., the pulse 128. The following records show the rise in blood pressure during the injection:

After	150	cc. it	was	96 mm.
"	250	"	"	110 "
"	400	"	"	128 "
"	500	"	"	132 "

As this pressure was deemed sufficiently high the injection was stopped. The patient's general condition improved at once, his radial pulse filling out and the rate dropping to 90. The following morning his blood pressure was 119 mm., his pulse 90. That afternoon the pressure rose to 128 mm. while the pulse dropped to 85. The pressure remained while the pulse gradually returned to normal. The patient made an uninterrupted recovery.

Case V.—(Dr. B. F. Alden, San Francisco.) M. C., a 35-year old native of France, because of an empyema of the left thorax following a lobar pneumonia, was transferred to the surgical service from the medical side May 20, 1913, for a thoracotomy. Before he was brought to the operating room the patient showed the weak, thready pulse, rapid respiration, extreme pallor, drawn face and cold and clammy extremities, ears and neck of profound shock. When placed on the operating table the patient seemed *in extremis* and was practically pulseless. Because of this no proper blood pressure reading could be made. The anesthetist advised against the use of an anesthetic. As it was agreed that the patient would die, 500 cc. of gelatin solution were injected into the median basilic vein. The incision was made without anesthetic as the patient was unconscious. Within ten minutes after beginning the perfusion a perceptible radial pulse was noted and this gradually improved in quality. A section of the eighth rib was now removed and drainage of the pleural cavity effected. The patient recovered consciousness while on the operating table and his blood pressure rose to 118 mm. It contained to mount until it reached 154 mm. the following day. At

the same time the pulse rate fell from 135 to 106. Two days later the pressure sank to 106 mm. while the pulse mounted to 136. As the drainage was found to be inefficient, by reason of adhesions in the pleura, the patient was reoperated under nitrous oxid and oxygen anesthesia. This was done without difficulty. The pressure then again rose to 126 mm. and remained there while the pulse fell back to 100. The patient's general condition gradually improved and after a prolonged convalescence he left the hospital.

It can, of course, be foreseen that what may actually be accomplished through gelatin transfusion in any case of low blood pressure depends upon the intensity, persistence and nature of the factors responsible for it. Viewed in this light, it is not remarkable that HOGAN'S experience thus far has seemed to indicate that cases of shock consequent upon simple hemorrhage are most easily relievable. Even those which showed extreme degrees of anemia rallied. Shock consequent upon injury or a surgical operation in the ordinary "clean" case seems to be controllable almost as easily. Least hopeful are the septic cases where the low blood pressure is in large measure dependent upon a heart suffering from the general intoxication. This is illustrated in Case VI:

CASE VI.—(DRS. W. B. COFFEY and C. A. WALKER, San Francisco.) Mr. C., a 32-year old laborer, was brought into St. Francis Hospital at 1 P.M. July 25, 1913, with the diagnosis of a ruptured typhoid ulcer. He had had typhoid since July 1. It was felt that the patient could not live through an operation. The blood pressure was 65 mm. and as it was believed that the patient would certainly die, an intravenous infusion of gelatin solution was started at 2 P.M. After 300 cc. had been injected the pressure rose to 90 mm.; after 400 cc. to 96 mm.; after 500 cc. to 99 mm. At this point the abdomen was opened under local anesthesia and found filled with fluid, fecal in character. The opening in the small intestine was quickly located and closed. The gelatin perfusion was continued during the operation, the blood pressure rising steadily even during operation as follows: after 600 cc. had been injected it was 106 mm.; after 700 cc. it was 108 mm.; after 850 cc. it was 108 mm. This higher pressure continued until 6.10 P.M. when he showed signs of a rapidly falling pressure and died.

In closing these paragraphs we would like to have it clearly understood that intravenous injections of proper colloid solutions are not at once to be accepted as panaceas for shock. In the clinical case every effort must be made to discover and meet the factors responsible for a weakened heart action, a lack of

tone in the blood vessels themselves (not as important as usually believed and then only terminally) and a diminution in the volume of the circulating blood. The monumental studies of YANDELL HENDERSON have taught that the last named is of great importance and determined, in good part at least, by an abstraction of water from the blood by the colloids of the tissues, which in conditions leading to shock develop an increased avidity for it. We have learned how such avidity may under normal circumstances and in œdema be decreased with alkali, salts and sugar, and so it is not surprising that this fact may be used to advantage both in the prophylaxis and in the treatment of shock.

Our discussion has thus far considered mainly the use of transfusion mixtures for a raising of the blood pressure in those simplest cases in which shock is the consequence of mere hemorrhage. We meet a threateningly low blood pressure also, however, under circumstances in which a diminution in the volume of the circulating blood is brought about by more indirect means. A loss in blood volume associated with a low blood pressure may follow injury or a surgical operation (traumatic or post-operative shock) and is a common finding in the acute or chronic poisonings (the toxemic shocks of the infectious diseases). Under all these circumstances it is not sufficient merely to fill up the blood vessels with more fluid, even if a proper colloid solution is used, but the conditions making for the low blood pressure must also be met.

YANDELL HENDERSON [1] has made the keen, and to us correct, suggestion that the decrease in volume of the circulating blood under such circumstances, which is the chief reason for the fatal issue, is brought about through an extraction of the watery constituents from the blood by the tissues. The tissues are able to do this in shock because, by a series of antecedent changes resulting in disturbances of their respiration, they have been brought into a state of oxygen lack followed by an abnormal production and accumulation of acids through which the capacity of the tissues to absorb water is increased. The tissues, therefore, take the watery constituents from the circulating blood and thus decrease its volume. If enough is taken out, a

[1] YANDELL HENDERSON: Am. Jour. Physiol., **27**, 167 (1910); where references to his earlier papers may be found.

critical point is reached which, once attained, is necessarily fatal, according to YANDELL HENDERSON'S views.

We are inclined to believe that the state of the patient under such circumstances is indeed a serious one, but we do not believe that it must necessarily prove fatal. It is not sufficient, however, in such cases to meet the low blood pressure through mere injection of a physiological salt solution or even a proper colloid mixture, for even the latter is in part robbed of its water, as is ordinary blood and by the same means. Even though colloid mixtures work better than simple salt solutions, it is necessary in all instances to overcome the tendency of the tissues to take the water from the blood. The principles that must guide us are simple enough. We need to neutralize the acids (and like compounds) which have been produced or which have accumulated in abnormal amounts in the tissues and to decrease their effects upon the tissue colloids, —in other words, we must reduce the swelling of the tissues. We do the former by giving the patients alkali, the second by the administration of salts. Both are easily accomplished in that we administer by mouth, by rectum or intravenously a properly prepared hypertonic sodium chlorid-sodium carbonate mixture.[1]

Through such procedures the tissues are kept from taking more water from the blood stream. As a matter of fact, they give off water which passes into the blood and so becomes available for secretion. The secretions which during shock have fallen in amount or perhaps have ceased entirely may therefore increase or begin anew. Through increase in blood volume the blood pressure also rises for a time. It may not, however, remain increased, for the reasons previously emphasized. The hypertonic salt solution with its sodium carbonate will work therefore for only an hour or two. When, however, we have succeeded in overcoming in this fashion the tendency of the tissues to extract water from the blood we may inject a proper colloid mixture, for it is now probable that this will be retained in the blood vessels and so maintain the blood pressure at a higher level for a longer period of time.

[1] See page 676.

3. Critical Remarks on Shock

I have allowed the above paragraphs to stand as originally penned because the Great War brought with it a renewed discussion of the nature of shock and its treatment. Innumerable papers have appeared on the subject, but scarcely any refer to what is written above or when such reference is made it is only for purposes of adverse criticism. This is a matter of interest because the authors of these papers in their practical recommendations bring forward only such as are the necessary consequences of the colloid-chemical notions of water absorption expressed above. While denying the theory, these authors therefore accept in their practical conclusions all the principles outlined above. Even when their misquotations of me are ignored and also the contradictions and self-contradictions in the work of the individual observers, they still agree among themselves on the following points.

The authors accept quite generally a low blood pressure as the criterion of shock. For its treatment they hold that a restitution of the volume of the circulating blood is the most important single element to be satisfied. To obtain permanent results a colloid solution of proper composition is demanded. As palliative measures they agree as being of assistance warmth, rest and food (particularly dextrose), air, delay in the use of general anesthetics, delay in the institution of major surgical operations, the administration of nitrous oxid-oxygen as the anesthetic of choice, and proper alkalinization. The Special Investigation Committee of the British Medical Research Committee,[1] for example, give as "practical corollaries" of their studies the following: (1) "Restoration of the volume of blood. . . is therefore the object to be aimed at." (2) "Transfusion of whole blood is probably the measure likely to have a successful result in the largest proportion of cases." (3) "Infusion of gum-saline solution will be almost as effective." (4) "Sodium carbonate may be given separately by mouth, rectum, or, if necessary, by cautious intravenous injection." (5) "Administration of bicarbonate might appear, therefore, to have some rational basis as a preliminary to operation."

W. B. Cannon[2] observes the shocked to show a low alkali reserve in the blood and recommends the avoidance of operations

[1] Bayliss, Bainbridge, Cannon, Elliot, Starling, etc.: Report No. 7. —Acidosis and Shock, 38, London (1918).

[2] W. B. Cannon: Jour. Am. Med. Assoc., **70**, 531 (1918).

upon such individuals. Later[1] with JOHN FRASER and E. M. COLWELL[2] under "preventive treatment" he recommends alkaline injections before operations (which he finds raise the blood pressure) and as the "ideal injection fluid for shock cases" a solution "with colloid added" preferring "one containing sodium bicarbonate and 6 per cent acacia." E. H. STARLING[3] thinks similarly, noting also that shocked individuals show "acidosis" as evidenced by a low alkali reserve which he holds should be combated with alkali, recommending for the purpose the intravenous injection of 500 cc. 2 per cent sodium bicarbonate with 5 per cent acacia. G. E. SUTTON,[4] in addition to mechanical fixation of broken bones, uses 2 per cent sodium bicarbonate injections and transfusion of whole blood in small amounts.

These ideas have all been expressed and employed for more than a decade past by my medical and surgical associates.

The observation of the various authors that simple sodium chlorid solutions, simple solutions of alkaline salts or hypertonic alkaline solutions produce only temporary alleviation or, in the case of the last named, an actual further fall in blood pressure contains nothing new.[5]

As the above paragraphs indicate, there is also nothing original in their suggestion that a hydrophilic colloid solution alone produces more lasting results. Under this heading, transfusion with whole blood is universally accepted as the best procedure when blood is available—as we ourselves first pointed out. The difficulties of always obtaining such has made imperative the consideration of substitute colloid mixtures. P. FIASCHI[6] and F. C. MANN[7] report satisfactory results following the injection of gelatin mixtures. C. C. GUTHRIE[8] found some colloid necessary

[1] W. B. CANNON, JOHN FRASER, E. M. COLWELL: Jour. Am. Med. Assoc., **70**, 618 (1918).

[2] JOHN FRASER and E. M. COLWELL: Jour. Am. Med. Assoc., **70**, 520 (1918); E. M. COLWELL: *ibid.*, **70**, 607 (1918).

[3] E. H. STARLING: Arch. Méd. Belges, **71**, 369 (1918).

[4] G. E. SUTTON: Brit. Med. Jour., **2**, 368 (1918); see also BRECHOT and CLARET: Bull. de l'Acad. de Méd., Paris, **79**, 404 (1918); G. BLECHMANN: Paris Médical, 8, 38 (1918); W. B. CANNON, Progrès Médical, **33**, 290 (1918).

[5] See page 483. Also C. H. NEILSON: Jour. Am. Med. Assoc., **60**, 436 (1913); JAMES J. HOGAN: Lancet-Clinic, **113**, 6 (1915).

[6] P. FIASCHI: Communication to the War Office and Admiralty of Great Britain (1915).

[7] F. C. MANN: Jour. Am. Med. Assoc., **71**, 1187 (1918).

[8] C. C. GUTHRIE: Jour. Am. Med. Assoc., **71**, 1607 (1918).

but preferred acacia. Other observers found gelatin to be no better than similar volumes of salt solution. Their disappointment must be attributed to the use of poor grades of gelatin or such as were contaminated with protein split products—the dangers of using which HOGAN and I pointed out years ago. W. M. BAYLISS, who as late as 1915 criticised adversely the colloid-chemical notions of water absorption,[1] accepts the whole theory in principle with his suggestion that 6 per cent acacia gum solutions be used to restore blood volume in shocked individuals.[2]

The palliative measures suggested are also old, being merely measures which either (1) prevent the development of acid and like products in the body or (2) tend to neutralize such as have been formed, so as to increase the margin of safety for the afflicted individual. Cold and muscular fatigue favor, for example, the development of lactic and other acids while warmth and rest inhibit such. Pain, all anesthetics and surgical operations also lead to acid intoxication. Even the substances used to save patients, like morphin, cocain, novocain, etc., by themselves act in this direction. When a general anesthetic must be employed, that which acts most quickly and which is subsequently lost most rapidly is obviously best, especially when associated with high oxygen intake,—hence the preference for nitrous oxid-oxygen anesthesia.

It is absurd to argue whether shock produces "acidosis" or "acidosis" produces shock. An abnormal accumulation of acid within the body (except in its first and small doses) is followed by vaso-dilatation, softening of the blood vessel walls and decrease in the effectiveness of heart muscle contraction. These things in their turn make for defective blood circulation and secondarily for more acid production in the tissues suffering from oxygen lack.

As substances similar to the acids in their action upon the colloids of the tissues, I have often stressed the amins. Peptone shock and histamin shock are examples of this class and BAYLISS' "wound shock," which he himself suggests as probably due to amins, falls in this category. At present we know only oxygen to

[1] W. M. BAYLISS: Principles of General Physiology, 100, 116, London (1915).

[2] W. M. BAYLISS: Intravenous Injection in Wound Shock, London (1918); Brit. Med. Jour., **1**, 553 (1918).

be of service in the destruction of these compounds and only high concentrations of various carbohydrates as effective against the action of these substances upon protoplasm. Hence the importance of a plentiful air supply and a charging of the system with carbohydrates.

PART FIVE

THE COLLOID-CHEMICAL THEORY OF WATER ABSORPTION AND SOME PROBLEMS IN BIOLOGY, PHYSIOLOGY AND PATHOLOGY.

PART FIVE

THE COLLOID-CHEMICAL THEORY OF WATER ABSORPTION AND SOME PROBLEMS IN BIOLOGY, PHYSIOLOGY AND PATHOLOGY.

I

TURGOR, PLASMOLYSIS AND PLASMOPTYSIS

In the earlier pages of this volume, when we were first placing our medically interesting problem of œdema, experiments were described which not only make this a problem of the cells, but it was pointed out that œdema really represents only one extreme of a series of phenomena common to all cells, vegetable as well as animal. To a brief consideration of these which are found grouped under the general headings of *turgor*, *plasmolysis* and *plasmoptysis* we shall now turn.

By turgor the plant physiologists understand the normal rigidity of the plant cell as determined by a normal or physiological water content. When by any means the protoplasm of the cell is made to shrink away from the morphological (cellulose) cell wall, the cell is said to be plasmolyzed. When, on the other hand, the protoplasm is made to swell so that the cell wall is ruptured, plasmoptysis is said to have resulted. The animal physiologists have not used these terms in such a strict sense. In the use of the term turgor they agree with the plant physiologists. The term plasmoptysis they do not generally employ at all, and under the heading of plasmolysis they not only consider all the more marked variations in the size of cells both in the way of a decrease or an increase, but also certain phenomena which

have become associated with such variations in size, as, for example, loss of coloring matter by the red blood corpuscles (hemolysis). These distinctions in terms must be borne in mind if confusion is to be avoided. To prevent ambiguity in the following paragraphs we will in each case first define our terms.

The reason why the phenomena of turgor, plasmolysis and plasmoptysis are brought up in this volume is because discussion of their essential nature has not as yet been brought to a satisfactory conclusion. For this reason the following paragraphs which bring a unifying explanation for many of the apparently disconnected and contradictory experimental facts bearing on the problem are not out of order. Again will we find ample evidence of the important rôle played by the colloids and thus see an application made to problems considered essentially physiological of certain principles which we have previously discussed under headings considered characteristically pathological.

II

ON THE ABSORPTION OF WATER BY SPERMATOZOA, EPITHELIAL CELLS AND WHITE BLOOD CORPUSCLES

In the attempt to establish the validity of the laws of osmotic pressure for certain physiological and pathological manifestations of water absorption, biologists have been particularly eager to work with material which on experiment was found to approximate most closely the behavior demanded by theory. It is for this reason that certain plant cells and the red blood corpuscles have been the subject of more exhaustive study so far as their behavior toward water absorption is concerned than any other cells. The reason why just these cells should have approximated obedience to the laws of osmotic pressure more perfectly than most others that have been studied may appear later. But even these chosen cells show such great exceptions to the behavior demanded by theory that it is impossible to escape the experimentally well-grounded conclusion that *most, if not all, cells do not follow the laws of osmotic pressure.* The attempts that have been made to harmonize the observed behavior of various cells with that demanded on the theory that cells represent osmotic systems are ingenious, but we can scarcely believe sufficiently supported

by experiment to be convincing. For the most part the explanations given are complicated, which constitutes in itself a threatening feature when the explanation of any natural phenomenon is hazarded. What strikes one as particularly encouraging about the colloid idea of water absorption is its simplicity, and the breadth of water absorption phenomena to which it may be applied without apparent experimental or theoretical objection.

In a preceding part of this book we tried to show how the absorption of water by the cells of muscle, the eye, the central nervous system, the kidney and the liver is essentially a function of their colloid state. *What was said regarding these cells is also true regarding spermatozoa, white blood corpuscles and the epithelial cells of the bronchi, intestine, bladder and esophagus.* We need not enter into the detailed experimental findings on this subject which may be found in H. J. HAMBURGER's [1] excellent work. We again encounter no difficulty in explaining the experimentally observed facts when we call to mind the effect of acids, alkalies, salts, and these in mixture upon the swelling of (hydrophilic) protein colloids. All the cells mentioned swell if placed in distilled water. This fact, which has always been interpreted as due to differences in osmotic pressure, is really to be explained by remembering that under the conditions prevailing in these experiments the cells produce acids which increase the capacity of their colloids for holding water. A second factor is found in the diffusion of at least some salts *out* of the cell, for the higher the concentration of the neutral salts in a colloid the less does it swell.[2]

[1] H. J. HAMBURGER: Osmotischer Druck und Ionenlehre; **3**, 2 to 33, 52; **2**, 400 to 432, Wiesbaden (1904).

[2] The question of the antagonism between acids and neutral salts has given rise to meaningless priority claims. In biological material it was first discovered by H. J. HAMBURGER: Arch. f. (Anat. u.) Physiol., 513, (1892); 153 (1893); Zeitschr. f. Biol., **28**, 405 (1891);. ibid., **35**, 252, 280 (1897), when he noted that it required a higher concentration of salt to prevent swelling and lysis of various body cells when acid was present than when such was not the case. He also noted that sulphates were more powerful in this regard than chlorids. HAMBURGER explained his findings in the terms of osmotic pressure saying, in essence, that the acid acted by increasing the intracellular osmotic pressure and that an increased salt concentration was therefore needed about the cell to counteract it. Other writers have since HAMBURGER's work claimed both the discovery of the fact and the explanation.

So far as I know I was the first to observe the general antagonism between acids (and alkalies) and neutral salts on the hydration capacity of protein

The direct swelling effect of acids, including carbonic, is readily understood. Acids always bring about the greatest amount of swelling in (protein) colloids, and they are found to do this also in this biological material. The effect of alkalies is variable. Sufficiently dilute alkalies inhibit the swelling of spermatozoa in water (through the combined effect of neutralization of the acid formed in the spermatozoa and the production of salts) and of epithelial cells and white blood corpuscles suspended in water, salt solution, sugar solution or serum. The alkali neutralizes the progressive production of acid in these cells, as this occurs under the conditions of the experiments (for example, separation from an adequate oxygen supply, as when the epithelial cells are scraped off a mucous membrane). In some concentrations and in some cells a greater swelling is produced by alkali than by any other chemical except an acid. The less evidence there is of a production of acids in a cell or a tissue used for such experiments as we are describing, the greater the power of alkalies to make them swell. This is because when much acid is produced the alkali is largely neutralized so that in the end we really observe the cells swelling in a low concentration of alkali with much salt (formed through neutralization); while when little or no acid is produced the cells are swelling in alkali with a little salt (that normally found in the cell). All the cells mentioned in this paragraph swell less in any salt solution than in distilled water. With every increase in the concentration of the salt there comes a progressive decrease in the amount of the swelling. At a certain concentration the cells maintain for a variable length of time what is considered their " normal " volume. If the concentration is increased beyond this they shrink. In this brief description are exemplified all that is contained in the terms plasmoptysis, turgor and plasmolysis as understood by the plant physiologists. Impossilbe as it is to understand these phenomena on the basis of osmotic pressure, equally easy is it to see in them a perfect parallel of (hydrophilic) protein colloids swelling in a dilute acid or alkali in the presence of variable amounts of different salts.

colloids (Am. Jour. Physiol., **20**, 330 (1907)), and to use this finding not only in the interpretation of biological observations like those of HAMBURGER but in the explanation of my own water absorption experiments. (Am. Jour. Physiol., **20**, 330 (1907); Pflüger's Arch., **124**, 69 (1908)).

The experimental observations on changes in cell volume upon which the just detailed conclusions are based were made by HAMBURGER in 1887, though they were not published until 1904, because the results did not fit in with the conception of the living cell as an osmotic system which HAMBURGER, like the plant physiologists, H. DE VRIES and W. PFEFFER, before him, was most interested in seeing established experimentally. The rôle of the colloids in accounting for the exceptional behavior of these various cells was, however, considered by HAMBURGER. Unfortunately he believed the latter a mere adjunct [1] to the biological importance of osmotic pressure, and not, as seems more correct, of *primary* importance—of such importance, in fact, that it not only relegates the rôle of osmotic pressure to a secondary place, but in most instances, if not all, questions its entire biological significance so far as water absorption is concerned. In a much more positive way has WOLFGANG PAULI [2] declared the swelling of white blood corpuscles in dilute acids and alkalies to be analogous to the swelling of colloids under similar conditions.

III

ON THE INTERPRETATION OF SOME EXPERIMENTS ON WATER ABSORPTION BY MUSCLE

It is well to return at this point to a consideration of certain experiments carried out by JACQUES LOEB and E. OVERTON on the absorption of water by muscle. While the experimental results of the two authors agree very well, their explanations of them are very different. As the views of neither have found general acceptance on account of the serious objections that can be raised against them, I would like to call attention to the harmonizing explanation that can be given of the observed facts on the basis of the colloid idea of water absorption as already discussed in a previous section [3] dealing with the absorption of water by muscle.

[1] " Die an der wasseranziehenden Kraft des Zellinhalts wenig betheiligten Colloidtheilchen," HAMBURGER, Osmotischer Druck und Ionenlehre, **3**, 4., Wiesbaden (1904).

[2] WOLFGANG PAULI: Ergebnisse der Physiologie, **6**, 126 and 127 (1907).

[3] See page 151.

If a frog's muscle is dropped into distilled water it suffers a progressive increase in weight. This phenomenon is usually interpreted as a response to immersion in a solution of too low an osmotic pressure, so that water is absorbed by the cell contents. I maintain that this is not correct, for were it, all our muscles ought to swell whenever we consume a quantity of fresh or distilled water, and a frog living in a fresh-water pond ought to do likewise. But this does not occur. Clearly the muscle swells only because removed from the body.

The difference between the muscle inside and outside of the body is this: Outside of the body the muscle develops acid, and in this and its effects upon the muscle colloids I would find the cause for the increased absorption, in distilled water. Added to this is the effect of the diffusion of salts *out* of the muscle, for the higher the concentration of salts in a (hydrophilic) protein colloid the less does that colloid swell in a dilute acid. Quite contrary to the generally accepted belief, a *loss of* the osmotically active electrolytes of a tissue may, therefore, distinctly *favor* the absorption of water. We will do well to consider this whenever we try to define wherein lies the "poisonous" effect of distilled water.

That the extirpated muscle develops acid must be borne in mind when we try to interpret the effects of acids, alkalies and salts upon it. To put a muscle into a dilute acid instead of into distilled water is simply to add the effects of the external acid to that produced spontaneously by the muscle. The effect of putting a muscle into an alkali must depend upon the concentration of the acid formed spontaneously in the muscle and the concentration of the added alkali. Depending upon whether the latter partially, entirely or more than entirely neutralizes the acid formed in the muscle we get as a final result the muscle swelling in a dilute acid plus certain salts, in a neutral solution of certain salts, or in an alkaline solution plus certain salts. As the amount of acid formed in a muscle is quite variable, and as in consequence the possibility arises of many differently concentrated mixtures of acid, salt and alkali, we have no difficulty in accounting for the large variation in results obtained when extirpated muscles are placed in dilute alkalies.

Interesting are the effects obtained when muscles are placed in solutions of various electrolytes or non-electrolytes. Let it

again be recalled that the extirpated muscle develops acid and that in consequence its colloids are really absorbing water in a medium containing acid as well as the salts or non-electrolytes. To consider first the electrolytes. OVERTON expresses surprise that while a 0.6 per cent sodium chlorid solution is in " osmotic " equilibrium with the red blood corpuscles of the frog, the muscle of the same frog demands a 0.7 per cent solution to keep it from swelling. The explanation is found in this: The muscle produces acid rapidly (within minutes to hours), while the red blood corpuscles do so only very slowly (requiring several hours to days). To counteract the earlier accumulation of acid in the muscle requires more neutral salt. The sodium chlorid solution that is customarily spoken of as a " physiological," " isosmotic " or " isotonic " salt solution for use with frogs' muscle is, therefore, one that is sufficiently concentrated to just prevent the swelling of the muscle through the production of acid that takes place within it. When now the " isotonicity " of different salts is determined it does not surprise us to find that this is not identical with their " isosmoticity," for the physiological coefficient is not identical with the physical one. On the osmotic conception of water absorption physically "isosmotic " solutions ought to be physiologically " isotonic." Yet experimentally this is not found to be the case. On the colloid basis of water absorption this result, of course, does not surprise us, for physically isosmotic solutions of different salts are not equally effective in reducing the amount of water absorbed by a (protein) colloid swelling in the presence of a dilute acid.

With every increase in the concentration of the salt solution we expect on the colloid basis a decrease in the amount the muscle swells. Experiment shows this to be the case. As we pass from the " hypotonic " solutions to those considered " isotonic " the muscle swells progressively less. If enough salt is added, the muscle not only does not swell, but shrinks to less than the volume of the freshly extirpated muscle. This marks the progression from the " isotonic " solutions to the " hypertonic." To explain these facts on the osmotic basis, OVERTON assumes the individual muscle cells to be impermeable to the salt. In the colloid theory the cells may be freely permeable, which, as a matter of fact, we know physiologically they must ye, otherwise it would be impossible to affect the behavior of muscle as

markedly as we can experimentally through various electrolytes.

Let us now turn to the non-electrolytes. OVERTON concludes that the muscle cells are permeable to practically all these. This conclusion, drawn from the fact that a long series of chemical compounds permit muscle to swell just as though they were not present, is undoubtedly correct, though it is not explained by saying that an osmotic membrane exists about the muscle cells which excludes salts while it is permeable to these non-electrolytes. The extirpated muscle again absorbs water because it develops acid when taken out of the body, and non-electrolytes in contrast to the electrolytes are, in the concentrations employed, practically without effect in antagonizing the action of the acid. These conclusions may be illustrated by citing two of OVERTON'S experiments.

(*a*) A sartorius muscle which has not changed in weight after some hours in a 0.7 per cent NaCl solution undergoes no change in weight if placed in a solution of 0.7 per cent NaCl containing 5 per cent methyl alcohol, in spite of the fact that the osmotic pressure of this mixture is equal to a 5.2 per cent NaCl solution.

OVERTON explains these facts by saying that in a solution of 0.7 per cent NaCl, the osmotic pressure within and without the cells is the same, and that while the osmotic pressure of the second solution is vastly higher than that of the contents of the muscle cell, it cannot become effective and withdraw water from the cell, because the methyl alcohol enters almost instantly into the muscle fibers. The correct explanation to my mind is this: The sodium chlorid solution has a concentration just sufficient to counteract the effect of the acid formed in the excised muscle, and so maintains the colloids of the tissues in a condition in which their capacity for holding water suffers no great change in the hours devoted to the experiment. As the non-electrolytes are practically without effect upon this, an addition of 5 per cent methyl alcohol to the pure sodium chlorid solution does not alter this absorption of water by the muscle.

(*b*) A sartorius muscle which is placed in a solution of 0.5 per cent NaCl plus 3 per cent methyl alcohol—a solution which has approximately the osmotic pressure of a 3.6 per cent NaCl solution—gains in weight just as though it had been placed in a pure 0.5 per cent (a somewhat hypotonic) NaCl solution. If

removed to a 0.7 per cent NaCl solution, the original weight is regained.

Our explanation of these facts reads as follows: The muscle gains in the NaCl-methyl alcohol mixture because the concentration of the NaCl is too low to keep the colloids of the tissues from swelling in consequence of the acid produced in the muscle after removal from the body, and so it absorbs water. The presence of the methyl alcohol is without effect because the non-electrolytes are practically without effect on the swelling of colloids in the presence of an acid. When the muscle is removed to the 0.7 per cent NaCl solution a concentration is encountered which counteracts the effect of the acid more completely, and since the taking up and giving off of water by colloids represent in large measure reversible processes, the muscle gives up some of its absorbed water and so assumes its original weight.

It is a simple matter, therefore, to account for the available experimental facts on the absorption of water by muscle on the colloid basis. Not only are the facts which it has been difficult to harmonize with the osmotic conception of water absorption explained in this way, but all the phenomena which we have been most willing to accept as osmotic may well represent only a fraction of that greater series of phenomena which we have designated as colloid. The question of whether the laws of osmotic pressure are at all applicable to the biochemistry of water absorption is therefore raised in the special case of muscle as it was previously raised in the case of spermatozoa, isolated epithelial cells, and white blood corpuscles.

That the laws of osmotic pressure, even as rendered more generally applicable to biological material through Overton's special assumptions, are incapable of accounting for all the observed biological phenomena, is admitted by this author himself, and in seeking an explanation of various aberrant phenomena he too considers the rôle of the tissue colloids. He refers, as did Pfeffer before him, to the part played by the imbibition water of the cells (Quellungswasser), and at one point, correctly to my mind, declares the swelling of muscle in dilute acids to be identical with the swelling of fibrin in dilute acids. But upon this colloid absorption he does not lay much weight, as is evident even in his latest writings.[1]

[1] See, for example, his article in Nagel's Handbuch der Physiologie, **2**, 2te Hälfte, 744 to 896, Braunschweig (1907).

It must be clearly understood that this questioning of the rôle of osmotic pressure in biological material so far as water absorption is concerned does not question its importance in the general problem of the diffusion of dissolved substances. This is an entirely separate problem. The advantage of the colloid conception of water absorption is that it permits of the diffusion of dissolved substances into regions where on the osmotic conception they could never get. As already pointed out, neither do my views affect or tend to minimize in the slightest the great biological significance of the law of partition as worked out by Hans Meyer and E. Overton in their experimental studies on the cell lipoids.

IV

ON THE NATURE OF HEMOLYSIS[1]

The important place which the teachings of colloid-chemistry find in the analysis of such a problem as that of hemolysis is indicated in these paragraphs. The commonest methods now known by which hemolysis (an escape of hemoglobin from the red blood corpuscles) may be brought about may be summed up thus:

(*a*) Through the addition of water to the blood, or through immersion of the red blood corpuscles in any salt solution having a concentration below a certain value (as ordinarily stated, below the osmotic concentration of the plasma).

(*b*) Through the addition of alkalies.

(*c*) Through the addition of acids.

(*d*) Through the addition of urea and certain other simple chemicals such as alcohol, acetone, and most ammonium salts. Most ammonium salts allow hemolysis to occur even when present in concentrations at which other salts do not permit it.

(*e*) Through putrefaction of the blood.

(*f*) Through electricity, but only under circumstances which allow of the formation of acids and alkalies in the solutions containing the corpuscles. This paragraph, therefore, constitutes only a subheading of *b* and *c*.

(*g*) Through heating the blood.

[1] Martin H. Fischer: Kolloid-Zeitschr., 5, 146 (1909).

(*h*) Through the addition of complex chemical substances, such as saponin, sapotoxin, bile derivatives, and snake venom. With these we must class the specific thermolabile hemolysins.

While hemolysis is easily produced by any of the methods outlined, the following difference is to be observed between the various methods. When a specific hemolysin, or a poison capable of acting at a very low concentration, is added to the blood, the hemoglobin escapes from the corpuscle, but the corpuscle undergoes no change in size. With few exceptions this is not the case in any of the other solutions—in all of them the red blood corpuscles increase in size when the concentration at which hemolysis occurs is reached. Especially marked is this increase in size in solutions of acids and alkalies in which hemolysis occurs very rapidly, and in which swelling is most pronounced.

It is not strange, therefore, that a causal connection has been sought between this escape of hemoglobin and the swelling of the corpuscle. In nearly all of the illustrations given, the two processes go hand in hand—it is generally stated that as soon as the red blood corpuscle swells it gives up its hemoglobin. It is not surprising in consequence that to several observers it should have seemed as though the only thing necessary for a complete understanding of the *physical* (not biological) half of this problem of hemolysis was a physico-chemical conception of the process of swelling.

Close study revealed that the salt solutions which just prevent the hemolysis of red blood corpuscles all have very nearly the same osmotic pressure, and so we find the theory advanced that the red blood corpuscles are surrounded by a semipermeable film, and that they swell or shrink, give up their hemoglobin or do not do so, depending upon whether the surrounding solution has a lower osmotic concentration than the corpuscular contents or the reverse. This conception is a purely mechanical one—as soon as the osmotic concentration of the fluid without the cell is below that of the cell contents, water passes into the cell, which in consequence swells. When this swelling has become sufficiently great, the corpuscle is rent asunder and the hemoglobin escapes.

As the number of experimental observations on the behavior of the red blood corpuscles has increased, more and more facts

have come to light which show that the laws of osmotic pressure, so far as this swelling is concerned, have only a most limited application to the problem of hemolysis, if any.[1] It is needless to recite all the objections here.

By way of illustration, it is enough to mention that isosmotic solutions of *all* salts and non-electrolytes do not at a certain concentration prevent hemolysis (ammonium salts, for example); that the amount of swelling of red blood corpuscles in isosmotic solutions of different salts and non-electrolytes is not the same; and that with the same salt the calculated decrease or increase in the volume of the corpuscle is not strictly proportional to the increase or decrease in the osmotic concentration of the surrounding medium. Certain of these objections have been met, at least in part, through OVERTON and MEYER'S studies on the lipoids. But even with the modifications introduced by these and other workers many of the phenomena observed, notably the action of acids or alkalies, cannot be at all explained on the osmotic basis.

If we call to mind once more the effect of various external conditions on the swelling of protein colloids, a ready explanation is obtained of most of the phenomena observed in hemolysis *so far as the changes in the size of the corpuscles is concerned.* Red blood corpuscles (or more correctly put, their stromas) swell most in solutions of acids or alkalies. This is also true of protein. The presence of various salts diminishes the amount that red blood corpuscles swell. The same is true of protein. Doubling the osmotic concentration of the salt does not halve the volume of the protein—the volume remains greater than half the original. Red blood corpuscles behave similarly. When isosmotic solutions are compared, red blood corpuscles are found to swell more in some than in others. We found the same to be true of protein. All these analogies seem to me to indicate that *the changes in the volume of the red blood corpuscles are dependent primarily upon changes in their colloids.*[2] *Those external condi-*

[1] See for example the careful studies of HANS KOEPPE: Arch. f. (Anat. u.) Physiol., 162 (1895); Pflüger's Arch., **62**, 573 (1896).

[2] WOLFGANG PAULI, Ergebnisse der Physiologie, **6**, 127 (1907), seems first to have considered it possible that the absorption of water by colloids and the absorption of water by red blood corpuscles are analogous. He does not discuss the matter of loss of color. More recently JULIUS KISS (Das periodische System der Elemente und Giftwirkung, Vienna (1909), only accessible as

tions which increase the capacity of the colloids for holding water cause red blood corpuscles to swell, and those which do the reverse, cause them to shrink.

It will be noticed that I have limited myself thus far to a discussion of the swelling and the shrinking of the red blood corpuscle, and have connected these processes in no synonymous way with the escape of hemoglobin from the stroma. This is because *I consider changes in the volume of the red blood corpuscles and the loss of hemoglobin by the stroma separate processes, which while they may often be associated, have really nothing to do with each other.* This conclusion is based upon the following facts:

When we attempt to construct a red blood corpuscle mentally, these points are of interest: *The red blood corpuscle is essentially a mixture of several colloids.* Of first interest is the protein body which is ordinarily said to constitute the stroma and which, from the way it becomes gelatinous in agglutination experiments, has been described as " fibrin-like " in character. Every one of its physico-chemical reactions betray it to be a hydrophilic colloid. Mixed with this stroma are the two lipoids, lecithin and cholesterin. According to R. Höber, the former of these particularly shows some of the pronounced reactions of the hydrophilic colloids (as witness its so-called "myelin reaction"). These two fat-like bodies have, however, a property not possessed by the protein portion of the corpuscle—they are good solvents for ether, chloroform, alcohol, and the remaining lipoid-soluble substances. A fourth important constituent of the red blood corpuscle is the hemoglobin. This, too, is colloid, even though most of the hemoglobins can be obtained with varying ease in crystalline form. A class difference, however, exists between hemoglobin and the other colloids enumerated as contained in the red blood corpuscle. Hemoglobin is not a hydrophilic, but a hydrophobic colloid; it is not a so-called emulsion colloid (emulsoid) as the protein constituents of the red blood corpuscle, or lecithin, but a *suspension colloid* (suspensoid).

What now is the nature of the combination between the various hydrophilic colloids (the stroma with the lecithin and cholesterin mixed in) and this colored "suspension" colloid? Hemoglobin cannot simply be *dissolved* in the red blood corpuscle, for the

a book review) comes to the same conclusion. Kiss, however, seems to consider swelling and loss of hemoglobin parallel processes. See above.

amount present is entirely too high. Neither can it be held in the corpuscle because this is covered by a semipermeable membrane. For reasons touched upon in discussing the biological significance of the analogy between the swelling of hydrophilic colloids and of protoplasm such a conception of the living cell is impossible. Nor is this membrane notion tenable in the modified form according to which it is made up of lipoids. The hemoglobin is contained in no such oil-covered sac, to flow out whenever this is dissolved or punctured. *The hemoglobin must be combined in some more or less fixed way with the rest of the corpuscle. The lack of evidence to show that this combination between stroma and hemoglobin is a chemical one, and the fact that an enormous amount of hemoglobin is held by a very small amount of stroma*[1] *leads me to assume that the combination between the hemoglobin and the rest of the corpuscle represents an adsorption phenomenon.*[2]

To test this hypothesis I constructed a system which simulated red blood corpuscles and tried the effect of different external conditions upon it. I used powdered fibrin stained deeply red with neutral carmine. This combination was chosen in order to obtain a hydrophilic colloid (fibrin) united with a hydrophobic colloid (carmine).[3]

As many, if not most, of the dyeing processes represent just such combinations between colloids, it would, of course, be an easy matter to choose other hydrophilic colloids, and other dyes, and depending upon their general and their specific properties, obtain results similar to and different from those which I obtained with my carmine-stained fibrin. I found, for example, that fibrin stained with hematoxylin behaves much like that stained with carmine.

The fibrin is stained by placing it in a beaker and covering it with a carmine solution. It is interesting to see how the fibrin absorbs enormous amounts of the dye. One has to add fresh

[1] Red blood corpuscles contain from 35 to 45 per cent solids, of which from 80 to almost 95 per cent (in man) consists of hemoglobin.

[2] See page 210. As generally held, this adsorption is a purely physical combination dependent upon the enormous surface presented by the adsorbing material. T. Brailsford Robertson has recently criticised this view and insisted that the combination might be chemical. It does not matter, so far as our argument is concerned, how this discussion is finally settled.

[3] My carmine solution was readily precipitated by salts, and was analyzable under the ultra-microscope.

dye time after time to replace that which the fibrin has taken up from the supernatant liquid.

The retention and loss of color by this carmine-stained fibrin is very similar to, and occurs under the same conditions as, the retention and loss of hemoglobin by the red blood corpuscle. This is readily apparent on comparing the following paragraphs with the similarly lettered ones given earlier in this section:

(*a*) If the red-stained fibrin is placed in water, the water slowly becomes red. In a solution of sodium chlorid, or in the chlorids, bromids, acetates and sulphates of sodium, potassium or lithium, this loss of color does not occur until after two or more days, when the supernatant liquid may become faintly pink.

(*b* and *c*) If a little of any acid or alkali is added to the colored fibrin, whether suspended in distilled water or in a solution of sodium chlorid, the loss of color occurs promptly. While the colored and powdered fibrin when suspended in salt solution has an opaque appearance, the bright transparency of a blood that has been laked is suggested after the carmine has come out. Upon standing for a little while the fibrin flakes sink to the bottom of the test-tube, so that the clear, transparent, red solution collects above the swollen uncolored " shadows " of the fibrin particles.

(*d*) Urea at any concentration brings about a prompt loss of color by the carmine-stained fibrin. Ethyl and methyl alcohol or glycerin act similarly, but not so powerfully. Solutions of ammonium salts also allow the stained fibrin to lose color in a way that the other salts do not.[1]

(*e*) I allowed some carmine-stained fibrin to putrefy in an uncovered dish. As the putrefaction progressed the supernatant liquid became more and more red.

(*f*) The effect of electricity was not studied.

(*g*) Gently heating some carmine-stained fibrin brings about a prompt loss of color.

(*h*) The effect of such substances as saponin, snake venom, etc., has not yet been studied.

The way in which red blood corpuscles lose their hemoglobin is not unlike the manner in which carmine-stained fibrin loses

[1] It is, of course, to be foreseen that were the carmine dissolved or adsorbed in a *lipoid*, the effect of the ethyl and methyl alcohols would be much more marked, and so imitate the phenomena observed in hemolysis yet more perfectly.

its red color in a dilute alkali. As is well known, red blood corpuscles when subjected to a hemolytic agent do not lose their coloring matter suddenly, but progressively. When ordinary blood is mixed with water the hemoglobin ring above the sedimented corpuscles slowly grows a deeper and deeper red. The same occurs with colored fibrin. In this simple fact is found a serious argument against any of the generally accepted mechanical conceptions of hemolysis which only postulate ruptured membranes and the escape of the hemoglobin contained within these membranes. Were the idea correct the escape of hemoglobin would always have to occur more or less suddenly, while we know it to be, as a matter of fact, a progressive affair.

Just as it has been found that an escape of hemoglobin and a change in the size of the red blood corpuscle (the stroma), while frequently associated, do not quantitatively parallel each other, so also can carmine-stained fibrin be made to lose or retain its red color entirely independently of the amount of change in the volume of the fibrin particles. The red fibrin swells enormously and promptly loses its color in a dilute alkali. The higher the concentration of the alkali the more rapidly and completely does the fibrin lose its color, yet so far as the swelling of the fibrin is concerned an optimal point is reached beyond which every increase in the concentration of the alkali only makes for a diminished absorption of water. Again, if a little ammonium chlorid is first added to the alkali, the loss of color is (practically) unaffected, and yet the fibrin swells but little. In other words, the swelling of the colored fibrin follows the laws which Gertrude Moore and I have previously laid down; the loss of color entirely different ones.

It seems to me that this analogy between the loss of hemoglobin by the red blood corpuscles and the loss of color by carmine-stained fibrin is more than accidental, and lends no mean support to the contention that the combination between hemoglobin and stroma is an adsorption phenomenon. If this view is accepted, then henceforth we will have to look for an interpretation of the phenomena of hemolysis into a different chapter of physical chemistry than that into which we have been accustomed to look.

Instead of fibrin and carmine, as already pointed out, any other hydrophilic colloid united with any other of the ordinary (colloid) dyes might just as well have been chosen. The majority

of these dyeing processes represent adsorption phenomena. We have also learned how these adsorptions may be increased, decreased or prevented altogether, as witness our use of the most varied mordants, precipitants, fixants and bleaches. Many of the methods thus employed (as the use of salts, acids, bases, formaldehyd, colloids of various kinds, heat, electricity, etc.) have a parallel in the ways and means by which the combination between hemoglobin and stroma may be increased or decreased.[1]

The relationships between the different colloids in the case of the red blood corpuscles are, of course, much more complicated than in the case of carmine-colored fibrin. In place of only two colloids, we have in the red blood corpuscle at least four, and this makes for an infinitely more complicated system. Not only may the adsorption characteristics of the individuals of a group of colloids toward any one other (hemoglobin in this case) be different, but they may mutually affect each other and so alter each other's adsorption characteristics. Lecithin and cholesterin, for example, have properties which allow them not only to share in, or modify the ordinary adsorption phenomena, as exhibited by the protein constituents of the red blood corpuscles, but because of their lipoid character they may not only absorb substances which the rest of the corpuscle cannot take up, but they may be affected by means which do not affect the rest of the blood corpuscle. Just in so far as these lipoids affect the relationship of hemoglobin to the protein constituents, or of hemoglobin to themselves, any substance capable of affecting the lipoids (chloroform, ether, acetone, etc.), must be able to influence the whole problem of the relation of the hemoglobin to the rest of the blood corpuscle, and so the problem of hemolysis.

[1] Oscar Berghausen showed me in Paul G. Woolley's laboratory in the University of Cincinnati, an excellent illustration of this. The hemolysis of human red blood corpuscles by carbonic acid can be markedly inhibited or prevented entirely by the addition of various salts. This explains why administration of properly selected salts (calcium salts and alkaline salts) tends to inhibit or stop the periodic destructions of the red blood corpuscles in paroxysmal hemoglobinuria, while the presence of acids (as after exposure to cold, compression of the blood supply, etc.) precipitates such attacks.

V

ON GROWTH AND SOME GROWTH PHENOMENA

The *turgor* of plant and animal cells is generally recognized as of such fundamental importance in growth and some of its associated phenomena, that the following remarks, which are intended to show how important a rôle the colloids may play in the whole problem, are perhaps not out of order.

Let us first consider the question of growth in general. As the term has been given various meanings by different authors during the past half century, it is well that we begin with a definition. Least open to objection is that of T. H. HUXLEY, who speaks of growth as " increase in size." C. B. DAVENPORT defines it more precisely when he regards it as " increase in volume." Objections to all other definitions arise from the fact that in them are too often included those changes which are better considered under the caption " differentiation." These changes, while they may serve as a necessary introduction to, accompaniment of, or consequence of growth, have really nothing to do with the process itself. DRIESCH's distinction between a " passive " growth due simply to the taking up of water and an " active " growth due to assimilation is excellent, though, as DAVENPORT has pointed out, the term "passive " is poorly chosen, for the taking up of water is by no means a passive process, and that part of growth in which water is absorbed usually gives far more palpable external evidence of its existence than that included under DRIESCH's heading of " active " growth.[1]

An objection that we might raise against HUXLEY and DAVENPORT's definition arises from the fact that not every increase in the volume of a cell, a tissue or an individual necessarily represents what is ordinarily regarded as growth. The development of an œdema in the extremities of an individual, the temporary swelling of a muscle after exercise, the imbibition of water by certain cells of the sensitive plant when touched, would all, according to HUXLEY and DAVENPORT, have to be regarded as " growth." In actual practice we would, of course, have little difficulty in distinguishing between true growth and the phe-

[1] See C. B. DAVENPORT: Experimental Morphology, 281 to 375, New York (1908).

nomena cited. What seems interesting to me is that in the end, when the physical analysis of these various physiological and pathological processes is complete, I believe we will find that what makes these processes overlap in definition makes them overlap in nature also.

The question to which anyone discussing the general problem of growth (increase in volume) is most desirous of getting an answer is this: *What is the source of the energy for growth?* That the energy set free is at times exceedingly great is clearly enough indicated by the every-day evidence of the enormous pressures exerted by the growing tips of roots and stems, and the direct measurements that have been made of the pressures exerted by woods, pulps and seeds when soaked in water. The greatest osmotic pressures that may be conceived in cells (assuming them, for example, to contain saturated solutions of substances of very low molecular weight) cannot account for more than a fraction of the observed pressures. *The pressures exerted by swelling colloids constitute an adequate source.* We need only to say how under the conditions in nature these pressures are rendered effective.

Let it first be called to mind that an absolute *sine qua non* for growth is the presence of water. How necessary is an adequate supply is evidenced by the farmer's worry about rain, and the laboratory experience of every worker in physiological botany. Secondly, all growth in volume is preceded by the production of various hydrophilic colloids. But not only are various colloids produced, but conditions which particularly favor the absorption of water by these colloids are also instituted. It is the rule, for example, that the growing tips of plants contain much acid. Many of them are sour to the taste and will even turn congo-red, blue. The rôle of acids in making various protein colloids swell is familiar to us from previous considerations. We have no difficulty now in understanding the observation long familiar to the plant physiologists (to whom we are indebted for most of our knowledge of growth) that there exist in the tips of plants three well-defined regions of growth.[1] At the extreme tip is found a region of rapid cell division with comparatively slow growth. Here is occurring a deposition of colloid material. Below this is found a region

[1] See DAVENPORT: Experimental Morphology, 283, New York (1908).

exhibiting great growth In this but little increase in colloid material is noted, but the greatest absorption of water. Why such a process should be found to consume much less time than the synthesis of colloid material in the tip explains itself. The third region again shows little or no increase in volume, but abounds in the changes collectively termed "differentiation." In plant cells a part of this differentiation consists in the formation of cellulose walls. As cellulose constitutes a colloid that is not affected by acids, bases, salts and various non-electrolytes at concentrations compatible with life, changes in the volume of adult cells (such as growth phenomena) are impossible. Only the colloid material within the cellulose membrane can be affected by these substances, in consequence of which it may shrink away from the cellulose membrane (plasmolysis) or swell to burst it (plasmoptysis).

The colloid conception of water absorption also gives us the means of understanding the mechanism of certain *growth curvatures* and *curvatures due to tropisms* of various kinds as manifested in plants and animals. The remarks that follow apply particularly to plants, in which Sachs first worked out the general problem of the tropisms, though they are just as applicable to many animals whose tropisms Loeb has shown to be identical with those demonstrated by Sachs in plants.

In consequence of the directive action of various external stimuli (light, heat, chemicals, electricity, water) the growing parts of plants bend and grow toward or away from the source of the stimulus (positive and negative tropisms). Growth curvatures may also evidence themselves in consequence of differences in the *intensity* of the action of external stimuli. Various explanations have been given of how these curvatures are brought about. In most the effect of *an increased growth*, as evidenced particularly *through the presence of an increased amount of water* in the convex portion of the plant stem or root, or the animal organism, over that of the convex portion, best explains the observed phenomenon. The question at issue now is how such an increased absorption of water by one side of a stem, for example, is brought about. Osmotic forces have been considered, but they are inadequate from both a qualitative and a quantitative standpoint. The phenomenon is quite easily understood on the basis of the absorption of water by colloids. We know, first of all, that

tropic curvatures both in plants and in animals are confined almost entirely to the actively growing parts, and of these, particularly to those regions in which various hydrophilic colloids are being produced most energetically (as in the tips of roots and stems where synthetic changes are most active). We know further, from the experimental studies of F. Czapek,[1] that under the "stimulus" of a tropism the chemistry of the stimulated protoplasm becomes entirely different from that of the unstimulated. Between these chemical differences, the hydrophilic colloids and an available source of water all the conditions are offered which lead to inequality in the swelling of the two sides of the vegetable or animal organism, with a consequent turning toward or away from the source of the stimulus. It also becomes intelligible why the older portions of a plant usually take no part in these tropic curvatures. The cells constituting them are surrounded by a (colloid) framework (such as cellulose) which is not affected by the slight chemical changes (low concentrations of acids, alkalies and variations in the distribution of various salts) that are capable of affecting so markedly the general body of younger cells and the cell contents of the older ones.[2] Through these more or less rigid cell walls both the expansion and the contraction of the adult cell is markedly hindered.

Our remarks show that in the last analysis various external stimuli produce their effects through chemical changes which they induce in the growing protoplasm. The effects of these external conditions come, therefore, to be referred to just such local chemical differences which we have long recognized as underlying the local irregularities in growth originating within the plant or animal itself. How important in this problem must be the production in different parts of the growing organism of different colloids (albumin, glycogen, starch, cellulose, lipoids, with their qualitative and quantitative differences in their capacity for holding water) or, with the same colloid, the localized production of acids, alkalies and salts is readily apparent. We can also see why, barring specific chemical effects, the action of electrolytes on growth should be so much greater than that

[1] F. Czapek: Ber. d. deut. Bot. Gesellsch., **15**, 516 (1898).

[2] See, for example, the experiments of Louis Kahlenberg and Rodney True: Botanical Gazette, **22**, 81 (1896), on the effects of acids, alkalies and salts on growth.

of non-electrolytes. Electrolytes affect colloids in comparatively low concentrations, while most of the non-electrolytes do not.[1]

These ideas on growth can be tested and many of its phenomena mimicked in the laboratory with a few colloids and various electrolytes and non-electrolytes. What must happen in these experiments can very naturally be foreseen, though the results are nevertheless interesting. With the use of cylinders, strips and leaves of gelatin various phenomena considered characteristic of the tropisms resulting from the action of chemicals, light, heat, etc., and certain irregularities in growth resulting from internal causes can easily be imitated in the laboratory. When such gelatin preparations are painted with a little acid on one side and are then dipped in water, beautiful negative curvatures are produced. If acidified gelatin is used and one side is painted with an alkali or a neutral salt, positive curvatures result. Or if a mixture of gelatin with egg albumin is employed a negative curvature results when a weak acid is employed, while a positive results if a stronger one (nitric acid) or a salt capable of coagulating the albumin is applied. When any dry acid (tartaric, oxalic) is stirred into gelatin in an irregular way and strips are then cut out of it and moistened with water, complicated curvatures, spirals and other irregularities in growth, such as characterize flowers, for example, can easily be obtained.

In conclusion, let attention be called to the ready explanation which the colloid conception of water absorption offers of the ways and means by which certain plants and animals protect themselves from loss of water. Aside from certain gross advantages of external form, protective covering, etc., it is known that plants possess internal mechanisms by which they protect themselves from loss when water becomes scarce. It is such mechanisms that enable the plants of the deserts and the dunes to maintain their existence. Certain aquatic strains of animal

[1] These colloid-chemical views on growth have found valuable support and development in the papers of K. Gedroiz (Russ. Journ. f. exp. Landwirtsch., **11**, 66 (1910)) and G. A. Borowikow (Biochem. Zeitschr., **48**, 230 (1913); ibid., **50**, 119 (1913) which show that the absorption of water by plants and their growth is governed by the laws controlling water absorption in simple colloids. More recent verification of the principles here laid down is found in the studies of D. T. MacDougal and his co-workers: Science, **44**, 502 (1916); ibid., **46**, 269 (1917); Proc. Soc. Exp. Biol. and Med., **15**, 58 (1917); ibid., **16**, 33 (1918); Proc. Am. Philos. Soc., **56**, 289 (1917); Hydration and Growth, Washington (1920).

and vegetable life are also possessed of such mechanisms, otherwise they could not withstand transference from fresh water to sea water, and vice versa. Through the work of VAN RYSSELBERGHE [1] we have learned that when water is scarce certain plants convert some of their starch into oxalic acid. Those types of plants which under natural conditions are most liable to suffer from lack of water (the succulents) seem all to possess the interesting property of reducing their output of carbon dioxid, while producing at the same time various organic acids as soon as subjected to unfavorable conditions for growth.[2] These phenomena of acid production have generally been interpreted as meaning that by such methods the plant increases the number of soluble molecules in its cell contents and so increases its osmotic pressure. A more correct explanation, it seems to me, is this—through the production of these acids the capacity of the plant colloids for holding water is increased, so that the agencies operating to rob it of this water are counteracted. A question that awaits an answer in the case of animals is whether a like production of acids is responsible here also for the maintenance of a normal water content, as when a fish, for example, born in fresh water moves out to sea.

The important help that the absorption of water by colloids can render the general problem of the ways and means by which the movement of sap can be accomplished and maintained, in trees for example, needs no specific comment.

VI

ON THE CONTRACTION OF CATGUT AND THE NATURE OF MUSCLE CONTRACTION [3]

The problem of muscular contraction naturally divides itself into three parts—a study of the physical changes that

[1] Quoted by HÖBER: Physikalische Chemie d. Zelle u. d. Gewebe, 2d Ed., 63, Leipzig (1906).

[2] Another means of protection against water loss resides in the conversion of crystalloid material into hydrophilic colloids, or colloids having a low water holding capacity into such as have a higher one. A splendid discovery in this direction is that of D. T. MACDOUGAL and H. A. SPOEHR (Year Book 17, Carnegie Institution, 85 (1918)) who found the leaves of desert plants to reduce their polysaccharids to pentosans (mucilages) as water was withdrawn from them.

[3] WILLIAM H. STRIETMANN and MARTIN H. FISCHER: Kolloid-Zeitschr., **10**, 65 (1912); Lancet-Clinic, **108**, 205 (1912).

characterize the muscular contraction, a study of the chemical changes that underlie this phenomenon, and lastly, that which is usually regarded as the most important part of the whole, the means by which the chemical energy regarded as the source of the muscular contration is converted into the mechanical. The physical changes of muscular contraction have by all odds received the greatest amount of study; next in order stand the chemical. Least agreement exists at the present time in the matter of how the chemical changes lead to the mechanical. It is more particularly toward the solution of this phase of the problem that these paragraphs are intended to contribute. What we have to say is best begun by detailing the results of a few experiments on the contraction of catgut.

1. Observations on the Contraction of Catgut

(1) As is well known since the classical studies of T. W. ENGELMANN,[1] it is possible to make raw catgut undergo alternately a marked shortening and an elongation by changing the character of the surroundings in which the catgut is placed. ENGELMANN found that catgut suspended in water shortened greatly when the water was heated, to lengthen once more when this was subsequently cooled. The following experiments show how such alternate contractions and relaxations may be brought about by other changes in the surroundings of the catgut.

(2) We prepared the catgut used in our studies from the commercial raw catgut sold to surgeons, or from violin strings, the material employed by ENGELMANN. The catgut strings were soaked in distilled water before being used, after which they were split into as thin strands as possible. One such strand may be used for an experiment, but, in order to get greater contractile force, it is best to use several, as shown in Fig. 132. Here four strands of catgut of uniform diameter have been fastened to the glass rod. It is best to wrap the glass rod with silk thread in order to keep the strands from slipping. The four strands are then gathered together at the bottom with a silk thread and the whole is fitted into a muscle lever such as physiologists use, arranged to write on a recording drum. The whole is set up in such a way as to make it possible to bathe

[1] T. W. ENGELMANN: Pflüger's Arch., 7, 155 (1873); Ueber den Ursprung der Muskelkraft, Leipzig (1893).

the catgut strands with any desired solution without in any way disturbing the apparatus, as indicated in Fig. 133.

(3) When a single strand of catgut, or a set arranged as described, has been permitted to absorb as much water as it will by being kept in distilled water (or in a "physiological" salt solution) no change occurs in the catgut, as evidenced by any movement of the lever, over long periods of time. The point of the lever writes a straight line. If we remove the beaker holding the distilled water and substitute for it another containing a dilute acid of some kind (lactic or hydrochloric is best) it is noticed that after a slight latent period the strands begin

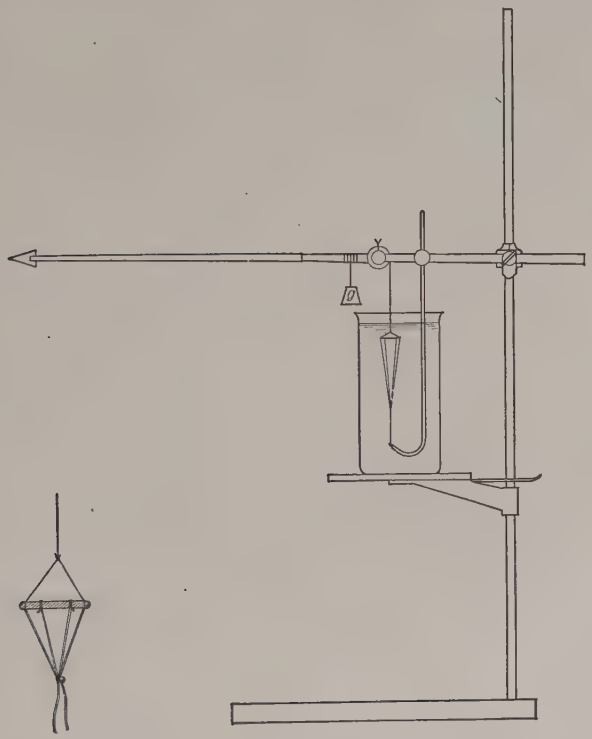


FIGURE 132.

FIGURE 133.

to contract and the lever point writes a a curve as shown in Fig. 134, I. After obtaining a maximal amount of shortening, a horizontal line is written as long as the catgut remains in the acid solution. If this is now taken away (indicated by the right-

hand arrow in Fig. 134 and the distilled water is replaced, the lever point begins to fall, and slowly returns to its old base-line level.

The height of the contraction is dependent in an interesting way upon the strength of the acid solution. Curve I of Fig. 134 was obtained by passing from distilled water to n/40 hydrochloric acid and then back to distilled water. Curve II was obtained in an identical way with n/60 hydrochloric acid, and Curve III with n/80 acid. These curves indicate that the greater the concentration of the acid, the higher the contraction. To this there is, however, an upper limit, n/40 hydrochloric acid representing very nearly the optimal one for the contrac-

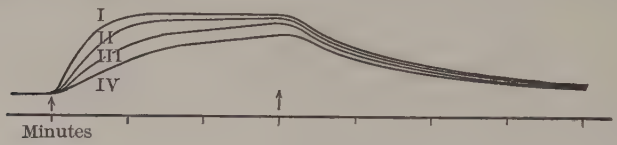


FIGURE 134.

tion of catgut strands. Curve IV, which is the lowest of the series in Fig. 134, was obtained with n/20 hydrochloric acid.

(4) The state of the catgut is of importance in determining the height of the contraction. Freshly soaked catgut gives the highest contractions. If the catgut is allowed to remain in distilled water for several days, the height of the contraction as obtained with a given concentration of acid becomes progressively less. This is shown in Fig. 135, where are recorded the contraction curves obtained with the same strands of catgut used

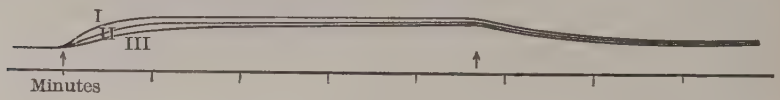


FIGURE 135.

to produce Fig. 134, after they had been kept in water for five days. As the recording lever, the weight carried, etc., were the same in both series of experiments, the two sets of curves may be compared with each other directly. Curves I, II, and III in Fig. 135 were obtained with the same concentrations of hydrochloric acid as those similarly marked in Fig. 134. What is the

nature of the changes in the catgut induced by prolonged immersion in distilled water we are not prepared to say, although we are most inclined to think them due to the digestion of the protein material, catalyzed in part no doubt by the ferments derived from the bacteria which get into the vessels holding the catgut in our ordinary laboratory experiments.

(5) Fig. 136 shows the effect of the thickness of the catgut strand upon the contraction. In this experiment only single strands of the same length could, of course, be used. The concentration of acid employed was n/40 hydrochloric in each case; *c* indicates the curve obtained with the thickest fiber, *a* that with the thinnest. It is readily apparent that the contraction occurs the more rapidly the thinner the fiber. Curve *a* is not as high as the other two. As the weight lifted was the same with all three fibers, such a result is easily accounted for on the basis of the relatively greater stretching force applied to the fiber in the case of *a* than in the case of the other two.

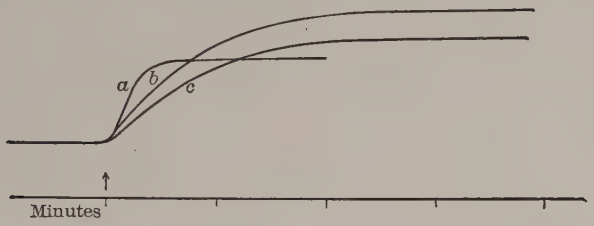


FIGURE 136.

(6) We noted above that catgut strands relax entirely when the acid solution in which they have contracted is replaced by distilled water. To get a complete relaxation, however, takes a long time. In other words, the fiber maintains a residuum of contraction. What this amounts to, after repeated transitions of the catgut from water to acid and back to water, is indicated in Fig. 137. On the first passing from water (base line) into n/40 hydrochloric acid the maximal contraction indicated by the first rise of the line is obtained. This is a record taken on a still drum. The first horizontal plateau records the maximal contraction, made by rotating the drum slightly forward. The fall in the record obtained on changing to water fails to reach the original base line. On

FIGURE 137.

again passing to acid the second rise is obtained, which it will be noted is higher than the first contraction. The second fall on immersion in water does not even reach the low point previously attained, and so on for a series as indicated in the figure. Then for a long period the contractions and relaxations remain equal, and there are no appreciable changes in the levels of the maximal and minimal points attained. But if the series of changes from acid into water and back again were kept up long enough, it is clear that the maximal points attained would become progressively lower and the amount of residual contraction diminish, due to changes suffered by the catgut (digestion?). Justification for such a conclusion is found in the differences observable in the contraction curves obtained from fresh and old catgut (Figs. 134 and 135).

(7) In Fig. 138 is shown the effect of adding various amounts of a neutral salt upon the contraction of catgut in an acid solution. Curve I shows the contraction of a series of strands when immersed in n/50 hydrochloric acid. The moment of immersion is indicated by the arrow *a*. At *c* the acid is replaced by water and relaxation results. Curve II was obtained by immersing the catgut at the point *a*, not in a pure acid, but in one containing in addition 0.25 per cent sodium chlorid, at the point *b* in a pure 0.25 per cent sodium chlorid solution, the relaxation occurring as indicated. Curves III, IV, V and VI were obtained in identical fashion by alternate immersion of the catgut in n/40 normal hydrochloric acid containing respectively 0.5, 0.75, 1.0 and 3.0 per cent sodium chlorid, and then in 0.5, 0.75, 1.0 and 3.0 per cent pure sodium chlorid. In Curve VI it will be noted that the power of the acid in bringing about a contraction has been suppressed entirely. As a matter of fact the fibers have contracted even less than in pure water (the curve lies slightly below the base line).

(8) The series of curves in Fig. 139 show an extremely interesting contrast to those of Fig. 110. Curve I is again a contraction followed by a relaxation as obtained by alternate immersion of the catgut in n/50 hydrochloric acid and in pure water. Curves II, III, IV, V, and VI were obtained by immersion in acid of the same concentration, but the solutions contained in addition respectively 0.25, 0.5, 0.75, 1.0 and 5.0 per cent sodium chlorid. At points lying between the arrows *b* and *c*, these solutions

FIGURE 138.

FIGURE 139.

were replaced by *pure water*. In every case further contraction is obtained before the relaxation sets in, which occurred immediately in Fig. 138 when we passed to salt solutions instead of pure water.

Results identical with those portrayed in Figs. 138 and 139 are obtained if any other acid (such as lactic) is used in place of the hydrochloric acid, or any other salt (such as sodium lactate) takes the place of the sodium chlorid. Neither is it necessary that the salt and the acid used have a common ion. Any salt will depress the contractions obtainable in any acid provided they do not react chemically with each other to undergo double decomposition.

FIGURE 140.

(9) In Fig. 140 the facts already noted in Fig. 139 are brought out in a slightly different way. In the first portion of the curve is noted the contraction obtained in a pure acid solution. Between the two points marked *Ringer solution* the catgut strands were immersed in this solution, after which water was substituted for it. As is readily apparent, one obtains under such circumstances a second contraction which is practically as high as that obtained initially.

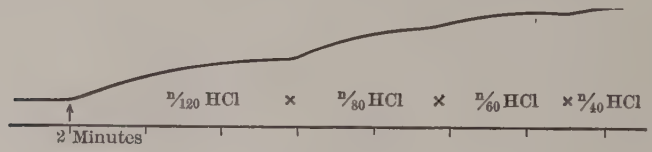


FIGURE 141.

(10) In Fig. 141 is shown the effect of immersion in successively greater concentrations of the same acid. In passing from one to the other a greater and greater contraction is obtained until a maximal one is reached in the highest (optimal) concentration of the acid.

(11) Thus far the relaxations of the catgut after immersion

in an acid have been obtained by using either water or a neutral salt. The relaxation occurs much more rapidly and the base line is regained sooner if for the neutral salt is substituted one that has the power of combining with the acid used to induce the contraction. The effect of this is shown in Fig. 142. In this case the contraction was obtained in n/2 hydrochloric acid, the relaxation in m/5 sodium bicarbonate solution.

2. Interpretation of Experimental Findings

It requires no imagination to see in Fig. 142 a duplicate of the tracing obtained when ordinary striated muscle is made to contract. But before we discuss this further let us see with what general phenomena in colloid chemistry we may correlate the above described experimental results.[1]

Catgut chemically considered is a protein, and its general physico-chemical reactions betray its colloid character. The fact that it swells in water at once serves to class it with the lyophilic colloids, or, as water is the absorbed substance, with the hydrophilic colloids. Merely superficial examination suffices, therefore, to place catgut in a group with gelatin, fibrin, gluten and serum albumin. But it behaves like these protein colloids in various other directions also. When we observe that on immersion in a dilute acid the catgut fiber contracts, we note at the same time that it does this by a process of swelling; it becomes thicker and shorter. The same thing is noted in the case of gelatin, fibrin, gluten or serum albumin. Gelatin, fibrin or gluten swell more in any dilute acid than in pure water, and the viscosity of serum albumin rises when acid is added to it. If the acid is washed out of these colloids, they resume their original form, as does the catgut when water replaces the acid solution. Just as gelatin, fibrin and gluten show within certain limits an increase in the amount of swelling with every increase in the concentration of the acid surrounding them, so also do we note an increased height of

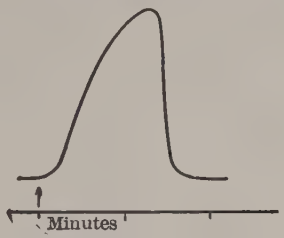


FIGURE 142.

[1] See page 61.

contraction in catgut when the acid concentration surrounding this increases.

The fact that catgut does not at once return to a previous state when the conditions about it are changed has its analog in the way in which fibrin, gelatin, etc., only slowly recover from the effects of a previous surrounding, when a new one is substituted for it (hysteresis).

With a given concentration of acid, the amount of swelling attained by gelatin, fibrin, gluten or serum albumin is reduced by the presence of any salt (even neutral salts, and such having no ion in common with the acid), and this reduction in the swelling is the greater, the stronger the concentration of the added salt. The parallel of this is found in the reduction of the height of the contraction of catgut in any acid solution, when any salt is added, the reduction being the greater the higher the concentration of the added salt. When fibrin has been allowed to swell to its maximum in a mixture of any acid with a salt, and is then placed in pure water, an initial increased swelling of the fibrin is noted, before the decrease sets in which brings the fibrin back to the degree of swelling characteristic of immersion in pure water. It is as though the acid were united more firmly to the protein colloid than are the salts. In spite of the greater diffusion velocity of acids over salts, the salts nevertheless seem to get out of colloid proteins more rapidly than do the acids, an observation not without biological importance, nor without interest for the theory of the colloid state. This behavior of fibrin also has its analogue in the already observed characteristics in the contraction of catgut when changed from a salt-acid mixture to pure water.

Point for point, therefore, *the contraction and relaxation of catgut* (*the absorption and secretion of water by catgut*) *is identical with the taking up and giving off of water by various other colloid proteins.*

It is easily seen how these experiments on catgut contractions correlate themselves with the experiments of ENGELMANN. What happens is identical in both instances, namely, an absorption and secretion of water by the proteins composing the catgut, only while ENGELMANN used an increase in temperature to make the catgut swell, we used, for purposes that will become evident immediately, various acids.

3. On the Analogy between the Described Contractions of Catgut and the Contraction of Striated Muscle

It is easily seen how similar are many of the curves illustrating these pages with the curves obtained and familiar to every physiologist when striated muscle contracts.

Fig. 142 could easily be mistaken for the record of an ordinary muscle twitch. In Fig. 141 we observe a series of successively higher contractions that remind us of the result when a series of inadequate stimuli are thrown at proper intervals into a striated muscle. Fig. 140 illustrates a phenomenon of rigor in catgut that EDWAD B. MEIGS has described in muscle. If a frog's muscle is immersed in a weak acid it goes into a state of continued contraction; if it is then placed in RINGER solution it relaxes, to contract a second time if it is subsequently placed in water.

The series of curves shown in Fig. 138 (and the first half of the curves of Fig. 139) illustrate in catgut what is called fatigue in striated muscle. The last half of the curves of Fig. 139 show again the contractions obtained in moving from an acid solution containing salt, into pure water as already referred to in Fig. 140. Fig. 137 illustrates the staircase phenomenon familiar from muscle physiology. Not only are the successive contractions of the catgut fiber progressively higher, but the fiber does not relax perfectly; there remains the residual contraction or increased tone familiar to us from muscle preparations. Fig. 136 shows how a catgut fibril may remain continuously contracted (tetanus). When we compare Figs. 134 and 135, and note how the same catgut fiber undergoes changes in its state which alter markedly its power to contract under given conditions, we recognize the analog of the importance of the state of the muscle in our physiological experiments as determining the character of its contraction.

The question now arises whether these physical analogies between the contraction curves written by muscle, and those written by catgut strings as described above constitute merely a happy coincidence, or whether the two processes are really in essence the same; in other words, *is the contraction of striated muscle a simple problem in colloid chemistry just as we found the contraction of catgut to be?* This is our belief. The anisotropic substance of the muscle corresponds to the catgut threads;

the isotropic substance or sarcoplasm to the water that surrounds the catgut threads.

But does our analogy between the contraction process in catgut and in muscle extend beyond these physical likenesses; in other words, are the *chemical* surroundings that we used to make catgut contract, identical with those that make striated muscle contract? This, we think, is also the case. In fact, we surrounded our catgut with the very chemical conditions which our present-day physiology holds to exist in muscle in the various phases of its contraction.

That a muscle produces acid during an ordinary contraction constitutes one of the classic facts of our physiology. This statement has only recently been generalized to the extent of saying that whenever a muscle is found to contract, evidence of acid production in the muscle exists. The contraction of rigor mortis is associated with the production of acid in the muscle, a fact which made L. Hermann, in calling attention to the analogies that exist between the contraction of muscle in rigor mortis and the ordinary muscle contraction, venture the suggestion that the ordinary single twitch was due to a temporary production of acid. More recently, particularly through the work of Fletcher, Hopkins and Meigs, it has been shown that in water rigor, heat rigor, chloroform rigor, etc., the contractions noted are also always associated with the production of acid in the muscle.

But not only is the production of acid associated with every contraction of muscle, it is the cause of this, as has been shown particularly well by McDougall and Meigs. McDougall studied the effects of acids and various other substances on the length of the isolated contractile elements of insect-wing muscle. He found these to shorten whenever he brought them in contact with any very dilute acid. With increasing concentration of the acid he found that an optimum was reached, beyond which a lessened contraction was observable. It will be recalled that we described the same phenomenon in catgut. When the muscle elements were removed from the acid solution to pure water, relaxation set in. The relaxation occurred more rapidly if instead of being placed in distilled water the muscle elements were placed in a sodium chlorid solution. The more highly concentrated this was the more rapidly did the relaxation set in. These facts also have their analogs in catgut.

MEIGS has greatly amplified the experimental observations of MCDOUGALL and described practically identical findings in frog's muscle.

From these remarks it is clear that the chemical conditions which we described above as effective in producing and modifying the contraction of catgut are identical with those which do the same in striated muscle, wherefore we conclude that *the phenomenon of contraction in muscle is entirely a problem in colloid chemistry.* If this conclusion is justified, then let us review briefly some of our current theories of muscular contraction with an eye to discovering which of them are most nearly correct. In so doing we shall find that the proponents of these theories erred not so much through a failure to recognize that muscular contraction represented a colloid problem, but rather in that they did not consider this explanation adequate or capable of accounting for more than a small part of the essential phenomena of contraction.

4. Historical and Critical Remarks

For the first great step toward the formulation of a colloid theory of contraction we are indebted to FRANZ HOFMEISTER,[1] that old master who has done so much to establish the biological importance of the colloid state. HOFMEISTER built upon the fact that protoplasm consists of a series of bodies which are capable of imbibing water, and pointed out how in the processes underlying the phenomena of imbibition a migration of water and the approximation of two points (contraction) that are surrounded by envelopes of water must occur whenever the imbibition capacity of the one is increased at the cost of the other. In this way he tried to account for all the special types of protoplasmic contraction as observed in different animal and plant forms.

The missing element in HOFMEISTER'S theory—which he himself points out—is that he could not explain why the colloids suffered the changes which make for the contraction; in other words, the nature of the chemical changes that induced the phys-

[1] F. HOFMEISTER: Die Lehre von der Pflanzenzelle, Leipzig (1867). Not accessible in the original.

ical. For a first suggestion in this direction we are indebted to T. W. ENGELMANN.[1]

ENGELMANN started from the well-known fact that during muscular contraction the carbohydrates and fats disappear from the muscle, while carbon dioxid, water, etc., appear in their place. This chemical change is associated with the liberation of heat, and this fact ENGELMANN utilized to construct upon it his thermodynamic theory of muscular contraction. Briefly formulated, ENGELMANN believes that the muscular contraction is initiated by a chemical change in the carbohydrates (and fats) of the muscle which results in the liberation of heat; this heat acting upon the contractile elements contained in the muscle (the anisotropic substance) makes them absorb the isotropic substance and so swell and shorten. The physical half of this theory, it will be noted, is also an imbibition theory of the nature of HOFMEISTER'S. To support this contention, ENGELMANN devised his now famous experiment in which he showed how catgut—which is also anisotropic—contracts in water when its temperature is raised, to relax again when the temperature falls. If the catgut strand is only momentarily heated, a contraction curve is obtained which is identical in appearance with a single muscle twitch.

ENGELMANN'S theory has been attacked on many sides, to our minds often with scant justice when the substituted theories are weighed in the balance against his. The best argument against it are furnished by two facts: First, the amount of heat produced during an ordinary muscular contraction is not sufficient to make anisotropic substance, of the nature of that found in muscle, shorten enough to explain a muscular contraction. Second, a contraction of muscle occurs under circumstances in which there may be no production of heat whatsoever. But even after all this is granted, the great fact remains that ENGELMANN was the first to create a satisfactory model of the muscular contraction out of materials which may be subjected to physico-chemical analysis, and so to remove the whole problem from a realm of speculation and terminology into one of reason and fact. As will be evident later, even in the matter of making a change in temperature responsible for the physical phenomena of contraction, he was

[1] T. W. ENGELMANN: See reference on page 452.

not entirely wrong; he only failed to pick the most powerful explosive out of a series lying before him.

The work of L. HERMANN constitutes a valuable contribution to the establishment of a colloid theory of muscle contraction in several directions. HERMANN emphasized very clearly the many analogies both from a chemical and a physical standpoint that exist between the ordinary muscular contraction and the various rigors. As " coagulation " is an obvious sign in the rigors, the question of whether the ordinary muscular contraction is a " temporary coagulation, or a kind of coagulation," has often been argued since HERMANN'S writings. HERMANN took the signs of coagulation and the contraction of muscle in rigor to represent evidences of one and the same process, and believed both of them to be due to the formation of acid in the muscle which occurs in all the rigors. In such a belief he was in part right, in part wrong. In making the production of acid responsible for both he was right, but to understand properly what happened beyond this point was impossible then, for colloid chemistry had not as yet developed sufficiently.

We know now that the obvious signs of any " coagulation " such as that which characterizes the rigors can only be associated with a *loss* of water by the " coagulated " colloid.[1] As the muscular contraction consists of an *absorption* of water, just the reverse of " coagulation," it is clear that *the " coagulation " and the contraction observed in muscle in rigor must be entirely separate processes.* What happens in muscle is identical with the development of a clouding in the cornea of an eye simultaneously with the swelling of the enucleated eye when this is placed in acidulated water,[2] or the development of a " cloudy swelling " in any of the parenchymatous organs when these are exposed to the same conditions.[3] *Two colloids at least are involved in the process, and while the one is behaving like gelatin, which swells in acidulated water, the other behaves like casein, which under the same circumstances is precipitated. In rigor the anisotropic substance swells under the influence of the acid and leads to the muscular contraction,*

[1] See WOLFGANG PAULI: Kolloid-Zeitschr., **7**, 241 (1910). PAULI and HANDOVSKY: Biochem. Zeitschr., **18**, 340 (1910). H. HANDOVSKY: Kolloid-Zeitschr., **7**, 183, 267 (1910); Fortschritte in der Kolloidchemie der Eiweisskörper, Dresden (1911). KARL SCHORR: Cited by PAULI and HANDOVSKY.

[2] See page 806; MARTIN H. FISCHER: Pflüger's Arch., **127**, 40 (1909).

[3] See page 540; MARTIN H. FISCHER: Kolloid-Zeitschr., **8**, 159 (1911).

while under the same circumstances another colloid is being precipitated (or, to use HERMANN'S *word, "coagulated") which gives the muscle an opaque appearance.* As we shall see later, the loss of water by the colloid which is being "coagulated" no doubt yields that necessary for the swelling (contraction) of the other.

Whether a rigor is reversible or not depends entirely upon whether the precipitation of the colloid involved is reversible or not; whether, in other words, removal of the condition which has made the colloid precipitate permits this to go back into solution. Depending upon the means employed to produce the rigor and the length of time it has acted, the colloid precipitations may or may not be reversible, and so the rigor.

This matter of rigor can, in a sense, also be mimicked on catgut. If we allow a chromium salt to act upon the catgut along with any acid, then we get not only a shortening of the catgut, but a permanent one.

While maintaining that acid production is responsible for the permanent contraction in rigor, HERMANN [1] made the further valuable suggestion that a *temporary* production of acid might account for the normal muscular contraction. But this remained a mere suggestion with HERMANN. The idea that the production of acid is responsible for the muscular contraction either under normal circumstances or in rigor has been particularly clearly enunciated by WILLIAM MCDOUGALL.[2] This author holds the anisotropic substance (the sarcomeres or contractile elements of the muscle) to be built up of tubules "having delicate walls and containing a fluid or viscid substance." The contraction he holds to be due to an absorption of fluid by these tubules "determined by the setting free of lactic acid in the fluid contents of the sarcomere, aided perhaps by an increase in the osmotic equivalent of these fluid contents through an increase in the number of molecules in solution. Then so long as the acid remains present in the fluid of the sarcomere, the additional fluid absorbed will be retained and the state of contraction will continue. But as soon as the acid escapes from the sarcomere the additional fluid will also escape with it into the sarcoplasm and allow relaxation to take place."

[1] L. HERMANN: Hermann's Handbuch der Physiologie, **1**, 255 (1879).
[2] WILLIAM MCDOUGALL: Jour. Anat. and Physiol., **32**, 187 (1898).

With McDougall's description of the histology of striated muscle we are not immediately concerned; in passing we would only point out that much of the discussion as to whether a histological structure is " solid " or " liquid " is purposeless, for animal and plant structures are chiefly colloid in composition, and the colloids that compose living matter combine in one the properties usually cited as characteristic of both the solid (maintenance of form) and the liquid state (surface tension, diffusion of dissolved substances).

It is clear that McDougall's ideas readily permit one to see why a single muscle twitch, a tetanus, or a rigor due to death, acid or water, all have the phenomenon of contraction in common. Underlying all of them is the production of acid in the muscle and depending upon whether this acid production is only temporary or permanent we have either a temporary or a continued state of contraction.

McDougall worked with isolated muscle fibrils. If these are placed in a weak solution of any acid (acetic or lactic) they swell and shorten. If they are then placed in distilled water and the acid is washed out of them they relax again. When the acid exceeds a certain optimal concentration the shortening becomes less marked. If any salt is present in the dilute solution of the acid, the contraction is lessened, or may not appear at all. If fibrils that have undergone no marked contraction in a solution containing both acid and salt are transferred to pure water, they undergo a rapid shortening. We need not re-emphasize that these statements are point for point identical with those we made above on the contraction and relaxation of catgut under similar circumstances.

The theoretical views of McDougall have found excellent experimental support and have won precision through the careful studies of Edward B. Meigs.[1] This author has not only collected the evidence which shows that an acid production underlies every phenomenon of contraction as observed in striated muscle, but he was the first to recognize and clearly express the fact that we deal in this problem (in part only, according to Meigs) with a colloid phenomenon, and that the acid

[1] E. B. Meigs: Zeitschr. f. allg. Physiologie, 8, 81 (1908); Am. Jour. Physiol., **22**, 477 (1908); ibid., **26**, 191 (1910); Jour. Physiol., **39**, 385 (1909).

owes its action to the fact that it makes certain colloids of the muscle swell.

Since MEIGS' writings MCDOUGALL[1] has also expressed this idea in unequivocal terms.

With this colloid view of the muscular contraction we heartily concur. The criticisms we have to make of MCDOUGALL and MEIGS' ideas are that on both theoretical and experimental grounds they do not consider the colloid conception entirely adequate. MCDOUGALL believes that in the process of contraction osmotic effects play a part in addition to the colloid, while MEIGS thinks, in his analysis of the nature of water absorption by striated muscle, that osmotic phenomena are concerned here. No experiments are cited by MCDOUGALL to support his osmotic hypothesis, and as MEIGS, who is the best champion of MCDOUGALL'S ideas, agrees that the swelling of the contractile elements in muscle (the essence of contraction) is a colloid phenomenon, we may consider it settled that at least so far MEIGS holds that osmotic phenomena do not play a rôle.

In maintaining that the "living" muscle is surrounded by osmotic membranes, MEIGS calls attention to the curve of water absorption exhibited by a muscle immersed in distilled water. Such a muscle rapidly attains a maximal swelling, then for a period loses in weight, gains in weight a second time, and then slowly loses again.[2] The curve representing the second gain in weight comes at the same time and accompanies the contraction of the striated muscle, and this MEIGS is willing to accept as a process of colloid swelling (swelling of the contractile elements under the influence of an acid). But the first swelling MEIGS does not consider as of the same type. He here follows the older belief of E. OVERTON, that osmotic membranes exist about the "living" muscle cell.[3] When excised and placed in distilled water, these osmotic membranes are destroyed, in part owing to the accumulation of acid within the muscle, in part due to differences in osmotic concentration inside and outside the muscle cell which lead to their rupture. When

[1] WILLIAM MCDOUGALL: Quarterly Jour. Exp. Physiol., **3**, 53 (1910).

[2] See page 155 of this volume; also MARTIN H. FISCHER: Pflüger's Arch., **124**, 69 (1908). E. B. MEIGS: Am. Jour. Physiol., **26**, 191 (1910).

[3] The same erroneous view is held by R. BEUTNER on the basis of experiments carried out under JACQUES LOEB'S direction. Biochem. Zeitschr., **39**, 280 (1912).

the membranes are thus destroyed, the fluid behind them is allowed to escape, and so the muscle loses temporarily in weight. But this temporary loss in weight can be interpreted more simply as a phenomenon in colloid chemistry. The muscle contains several colloids, and the maximal swelling and precipitation points for any given set of conditions are not the same for all these colloids. Under the influence of an acid, for example, the maximal swelling of the one may therefore be attained and exceeded sooner than that of another, and so a swelling of one colloid in the muscle may have reached and gone beyond its maximum (an increase followed by a decrease in weight) before another has attained its maximum. As a matter of fact we know that just such a relationship must exist between the different colloids in a striated muscle when this contracts normally. There is no free water in the body; it is all held in combination with the colloids of the tissues.[1] If one colloid element in an organism swells (say the anisotropic substance), it can do this only as it first robs some other element of its content of water. It would be eminently useful, therefore, if the conditions which on the one hand make for a swelling of the anisotropic substance, on the other make for the shrinkage (giving up of water) of another (isotropic substance).

To our mind all that characterizes the phenomena of water absorption and of contraction, or the loss of water and of relaxation in muscle, together with the various phenomena of " coagulation " observed in the rigors, represent but simple expressions of the effect of various acids and salts on that mixture of the several protein colloids which make up the muscle. We propose shortly to deal further with this subject. Here we would only direct attention once more to Fig. 140 and the apparently complicated series of reactions that may be obtained from a simple catgut fibril when exposed to the action of water, acids and salts. It is reactions of this type in muscle cells that have given rise to the highly complicated beliefs regarding the existence of membranes, etc., in and about them. As a matter of fact, we have no more reason for postulating their existence in muscle than in our catgut.

Much of the confusion that exists to-day in this whole problem of contraction, water absorption, irritability, etc., as observed

[1] See page 296; also Martin H. Fischer: Kolloidchem. Beihefte, 2, 304 (1911).

in muscle, arises from the fact that various authors have too carelessly passed from observations made on one to conclusions regarding another, instead of studying each phenomenon separately. Association of phenomena does not make them identical. Just as we learned that the signs of coagulation observed in rigor mortis are not identical with the phenomena of contraction observed in the same condition, so also does water absorption not parallel loss of irritability, or loss of irritability mean a loss of the power of contraction.

When the original report of these observations on catgut was in press, the colloid-chemical theory of muscular contraction upon which they bear received valuable and independent support through the work of VON FÜRTH and LENK [1] on rigor mortis. In a careful and convincing study of this problem these authors show that the postmortem contraction of muscle is a colloid process and influenced by various external conditions in the same way and in the same direction as the swelling of proteins. Somewhat later WOLFGANG PAULI [2] discussed the general problem of muscular contraction and in bringing fresh support for the colloid theory of contraction further illuminated the subject by a critical discussion of the chemical changes which induce the colloid ones. Independently of these authors, J. GROBER [3] has shown how the rate of swelling in simple colloids approximates the rate of the muscular contraction and quite recently RUDOLF ARNOLD [4] has studied the water absorption and the contraction of different kinds of human muscle in a way which brings new and corroborative evidence of their essential colloid-chemical character.

[1] VON FÜRTH and LENK: Biochem. Zeitschr., **33**, 341 (1911).
[2] WOLFGANG PAULI: Kolloidchemie der Muskelkontraktion, Dresden (1912).
[3] J. GROBER: Münch. med. Wochenschr., 2433 (1912).
[4] RUDOLF ARNOLD: Kolloidchem. Beihefte, **5**, 411 (1914).

PART SIX

NEPHRITIS

PART SIX

NEPHRITIS

I

THE THESIS

As apparent to the most casual student, our ideas regarding the nature and cause of nephritis are to-day in a state of chaos. The reasons for this are not far to seek. While physiology, pathology and clinical medicine have all contributed toward the analysis of the problem, little or no effort has been made by the various workers in each of these fields to find common ground with those in another. Such effort needs to be made, for, as pointed out above, we step in no abrupt manner from the physiology of the kidney into its pathology, or from laboratory findings into the practical problems of everyday medicine.

We need in these pages to get a definition of nephritis which is sufficiently broad, and so we shall use this much-abused term in its ordinary clinical sense. It becomes therefore a convenient heading under which to consider those clinical pictures which are characterized by the appearance of casts and albumin in the urine; by certain morphological changes in the kidney; by a change in the amount of water put out by it; by changes in the absolute and relative amounts of dissolved substances given off in the urine, and by such associated phenomena as œdema, increased blood pressure and cardiac hypertrophy. How these all fit together will develop later.

I need not be reminded that the term nephritis with its implied meaning of an inflammation of the kidney is a misnomer,

because in the "non-purulent inflammations of the kidney" which constitute the accepted of the nephritides, the ordinary pathological evidences of inflammation are largely missing. Terminological discussions do not change nor yet analyze the well-recognized pathological conditions with which we are dealing.

That which we as clinicians have come to regard as a clinical entity, and call nephritis, represents in reality the aggregate of a number of changes each of which must be treated separately if we would come to a satisfactory understanding of what is included under the clinical term. At least silently, the necessity for such a division of the subject has, as a matter of fact, long been recognized, for have we not largely given up the discussion of nephritis and taken up more and more that of albuminuria, anuria, œdema, chlorid retention—all of them *parts* of nephritis? Yet the persistence of the term nephritis in spite of our daily efforts in medicine to become scientifically more precise seems to be not without reason; it is the one term by which we are enabled to express the fact that the albuminuria, the anuria, etc., nearly always appear as *associated* phenomena. But from such a constancy in association we are enabled to draw an important conclusion—*they must all have a common cause.* The following pages attempt to show what this is.

To render our argument clear, we will at once state our general conclusion:

All the changes that characterize nephritis are colloid-chemical in nature and due to a common cause—the abnormal production or accumulation of acid and of substances which in their action upon colloids behave like acid, in the cells of the kidney. To the action of these upon the colloid structures that make up the kidney are due the albuminuria, the specific morphological changes noted in the kidneys, the associated production of casts, the quantitative variations in the amount of urine secreted, the quantitative variations in the amounts of dissolved substances secreted, as well as the other signs of nephritis which appear in direct connection with the kidney. The alleged consequences of kidney disease such as œdema, high blood pressure, uremia, etc., are not consequences, but accompanying signs and symptoms which demand separate discussion and analysis.

We shall now take up the proofs for these contentions in order. It is convenient to consider first the chemical factors

which bring about the colloid changes, and of these we shall lay main stress on the abnormal production or accumulation of acid in the kidney. Not only does this seem to be the most important, but our remarks concerning it may serve as an outline by which the value of any other factor in the problem may subsequently be tested. If our thesis is correct we must be able to show that:

1. There is evidence of an abnormal production or accumulation of acid in the kidney, or of conditions predisposing thereto in every case of nephritis; and conversely that:

2. Any means which leads to an increased production or favors the accumulation of acid in the kidney results in nephritis.

II

AN ABNORMAL PRODUCTION OR ACCUMULATION OF ACID IN THE KIDNEY OCCURS IN EVERY CASE OF NEPHRITIS

§ 1

If nephritis results whenever the acid content of the kidney is sufficiently increased then evidently the maintenance of its normal state must be intimately associated with maintenance of *neutrality* in it. We are therefore, first of all, interested in the fact that (exclusive of the gastric juice, the urine, and less positively, the sweat, vaginal secretion, and alimentary contents when fat is fed) *the fluids and tissues composing the normal mammal are to all intents and purposes neutral in reaction and are capable of maintaining this neutrality against the introduction of considerable acid into them.*

In the terms of our modern physical chemistry and accepting for the time being the generally held notion (to which we do not ourselves at all subscribe [1]) that cells and body fluids (like blood) are "solutions" which may be compared to the dilute solutions of the physical chemists, an acid reaction is due to the presence of free hydrogen ions, an alkaline reaction to the presence of free hydroxyl ions. A neutral reaction means, therefore, one of two things: either neither of these ions are present, or else just as many of the one as of the other, so that they balance each other.

[1] See pages 52 and 775.

The claim that the blood is neutral (and from this it has been generally assumed that the tissues themselves are also neutral in reaction) may at first sight occasion surprise when considered in the light of our older teachings that the body fluids and the cells are "alkaline." But these older conclusions were based upon results obtained with titration methods. The blood, for example, was held to be "alkaline," because it is capable of neutralizing acid. But the power of a solution to neutralize an acid is not an index of its content of free hydroxyl ions which alone the modern physical chemists accept as the true measure of its alkalinity. Such hydroxyl ion measurements upon the blood (and the tissues) were first made by P. Fraenkel,[1] G. Farkas,[2] and Rudolf Höber.[3] The observations of these authors agree in *pronouncing the normal blood neutral in reaction; as neutral as pure distilled water.*

Of further interest is the fact that *this state of neutrality of the blood (and of the tissues) is maintained against the introduction of considerable acid or alkali into them.* When exposed to the action of an acid, it is found that the normal hydroxyl ion concentration of the blood drops with the progressive introduction of acid into it, in the form of a curve, which falls only very slowly at first, and then more rapidly. Just why and how the state of neutrality is thus maintained does not at this particular moment interest us, but it may not be amiss to point out that two factors are involved in the process. The first lies in the fact that such salts as sodium carbonate and disodium hydrogen phosphate are capable of uniting with acids (carbonic and phosphoric acids) to form salts having a higher hydrogen content (sodium bicarbonate and sodium dihydrogen phosphate), but which in their dissociation yield few more *hydrogen ions* than the salts from which they were originally formed and which were present in the blood to start with. In other words, there is only a slight increase in the concentration of the hydrogen ions (increase in hydrogen ion acidity) in spite of the considerable introduction of acid into the system. (L. J. Henderson.)[4]

[1] P. Fraenkel: Pflüger's Arch., **96**, 601 (1903).

[2] G. Farkas: Pflüger's Arch., **98**, 551 (1903); Arch. f. (Anat. und) Physiol., Supplement, 517 (1903).

[3] Rudolf Höber: Pflüger's Arch., **81**, 522 (1900); **99**, 572 (1903).

[4] L. J. Henderson: Am. Jour. Physiol., **15**, 257 (1906); **21**, 169 (1908); **21**, 427 (1908); Ergebnisse d. Physiologie, **8**, 257 (1909), where extensive references to the literature will be found.

The other and perhaps lesser element for the maintenance of neutrality resides in the amphoteric character (that is to say their power of combining either with acids or alkalies) of the colloids found in the blood and tissues. The albumins, for example, can unite with considerable quantities of acid (or alkali) without any decided change in their behavior toward indicators. The presence of certain colloids in any system will therefore serve to delay the increase in the concentration of the hydrogen ions when an acid is added to this system.[1] *But let not the impression be gained from these remarks that blood or the tissues are not sensitive to even very minute additions of acid (or alkali) to them. Such an increase in the concentration of the carbonic acid as occurs when normal arterial blood becomes venous is already sufficient to reduce the hydroxyl ion concentration in the latter to one-half that existing in normal arterial blood. How profoundly even such a change affects the state of the colloids we will have occasion to discuss later.* For the present we are content with making the point that the blood and (presumably) the tissues are neutral in reaction and that they are capable of maintaining this neutrality within rather wide limits, even when subjected to the action of an acid.

§ 2

As modern physico-chemical studies have reduced what we formerly regarded as the "alkalinity" of the blood to a point where we may call it neutral, so also have they reduced the normal "acidity" of the urine from what we used to assume this to be. Just as the neutralizing power of the blood for acids is not accepted as a true indication of its reaction, so also is the amount of alkali with which a given specimen of urine will combine no longer accepted as a measure of its true acidity. To gage this properly the concentration of the hydrogen ions in it must be determined and this was not done until L. von Rhorer[2] and Rudolf Höber[3]

[1] J. Sjöquist: Skand. Arch. f. Physiol., **5**, 277 (1895). Otto Cohnheim: Zeitschr. f. Biol., **33**, 489 (1896). K. Spiro and W. Pemsel: Zeitschr. f Physiol. Chem., **26**, 233 (1898). S. Bugarszky and L. Liebermann: Pflüger's Arch., **72**, 51 (1898). T. B. Robertson: Jour. of Physical Chem., **11**, 542 (1907) ibid., **12**, 473 (1908).

[2] L. von Rhorer: Pflüger's Arch., **86**, 586 (1901).

[3] Rudolf Höber: Hofmeister's Beiträge, **3**, 525 (1903).

applied the principle of the gas chain to the physico-chemical analysis of the urine. Table CII, taken from HÖBER,[1] indicates what is the concentration of the hydrogen ions in a series of *normal* morning urines.

TABLE CII

NORMAL URINE

Hydrogen ion acidity (10^{-5}·CH).	Titration acidity.
0.58	0.046
0.52	0.034
0.50	0.042
0.46	0.069
0.31	0.075

It would support our idea of the cause of nephritis if it could be shown that *this acidity of the urine increases in conditions associated with the urinary findings characteristic of such kidney disease*. How strikingly true this is, is clearly evident from the analyses of *nephritic* urines given in Table CIII also taken from HÖBER and made, of course, without thought of using them for such purposes as we do here.

TABLE CIII

ABNORMAL URINE

Hydrogen ion acidity (10^{-5}·CH).	Titration acidity.	Remarks.
2.34	0.019	
1.50	0.018	Interstitial nephritis.
0.84	0.027	
1.10	0.020	
2.20	0.022	Acute nephritis.
2.10	0.020	
0.56	0.014	Chronic interstitial nephritis.
0.67	0.050	

As is seen on comparing the two tables, the active acidity of the urine of nephritics may be more than four times that of the normal urine. But Table CIII already suffices to betray another fact. *The highest acidities occur in the acute forms of nephritis, in other words, in the same forms in which we find most albumin, the largest number of casts, the greatest decrease in the*

[1] RUDOLF HÖBER: Physikalische Chemie d. Zelle u. d. Gewebe, 2d Ed., 158, Leipzig (1906).

urinary output, etc. The lowest values are found in the chronic interstitial forms, in other words, in the very types in which albumin is found in smallest amounts, or at times not at all. The degree of the albuminuria and the other evidences of kidney disease therefore tend to follow the degree of acidity. We shall have occasion to return to this question later.

Let us now look at the columns in these tables that record the *titration* acidities. It is such determinations that we find recorded in large number in clinical studies of nephritis. When the individual titration acidities in the above tables are compared with their corresponding hydrogen ion acidities, it is readily apparent that the two values do not even approximately parallel each other. What is learned when the titration acidity of the urine is determined, is its *capacity to neutralize alkali. Under otherwise constant conditions* it is clear that this titration acidity of the urine must grow with every increase in the amount of acid in the urine. *The uniformly higher titration acidity of the urine in nephritis,* as shown not only in tables CII and CIII, but in the scores that may be found in any of the larger monographs on nephritis, *becomes further evidence, therefore, in favor of our contention that an abnormal production or an abnormal accumulation of acid occurs in the kidney when thus affected.*

§ 3

In the same way that we use the increased capacity of the urine for neutralizing alkali as evidence for the presence of abnormally large amounts of acid in it (and so in the kidney cells from which this comes), so also may we use the decreased capacity of the blood for taking up acid as evidence in the same direction. The titration values of the blood, which the earlier clinical observers looked upon as indices of its "alkalinity," may be drawn upon for evidence to show that in the nephritides there exists a decreased power of the blood to neutralize acids. As studied particularly by Rudolf von Jaksch,[1] W. H. Rumpf,[2] E. Peiper[3] and F. Kraus[4] *a decrease in the acid capacity of*

[1] R. von Jaksch: Zeitschr. f. klin. Medicin, **13**, 350 (1887).
[2] W. H. Rumpf: Centralbl. f. klin. Medicin, **12**, 441 (1881).
[3] E. Peiper: Virchow's Arch., **116**, 337 (1889).
[4] F. Kraus: Zeitschr. f. Heilkunde, **10**, 106 (1889); Arch. f. exp. Path. u. Pharm., **26**, 181 (1889).

the blood is noted in no conditions more strikingly than in nephritis and its oft associated "uremia."

§ 4

Our argument thus far has shown that in nephritis there is a great increase in the hydrogen ion acidity of the urine, and that in both the urine and the blood there occur changes in the titration values which clearly indicate that both are holding a more than normal amount of acid. Our knowledge of physical chemistry (the laws of chemical equilibrium) permits us to utilize these facts as evidence indicating that the kidney itself, in other words, everything which lies between the urine on the one hand and the blood on the other must, under such circumstances, also shows an increased acid content. But it would strengthen this view if we could bring more direct proof in support of this deduction. It would be well, of course, if we could obtain a direct measure of the hydrogen ion concentration in the kidney. Gas-chain methods are naturally not applicable to solid organs, and to apply them to the expressed juice of the kidney would be to introduce so many errors into the whole prolbem as to render the conclusions valueless. We can, however, obtain material help by using indicators.

Proof of an increase in the amount of acid held by the kidney cells in conditions associated with the urinary findings of nephritis is furnished by the following facts:

In 1885 H. Dreser[1] described a series of experiments on the excretion of dyes by the kidney which differed from the preceding studies of this subject as first made by R. Heidenhain[2] and M. Nussbaum,[3] in that he utilized the results of his experiments in an attempt to get an answer to the question as to where in the kidney the acid of the urine is secreted. Dreser made chief use of acid fuchsin which he injected in 5 to 10 per cent solutions (amounts not stated) into the dorsal lymph sacs of frogs. This dye has the property of being red in aqueous solution only in the presence of an acid; in an alkaline solution it becomes practically colorless (yellow). Dreser therefore reasoned that the presence of a red color in any tissue after the in-

[1] H. Dreser: Zeitschr. f. Biol., **21**, 41 (1885); ibid., **22**, 56 (1886).
[2] R. Heidenhain: Pflüger's Arch., **9**, 1 (1875).
[3] M. Nussbaum: Pflüger's Arch., **16**, 141 (1878).

jection of this dye into the circulation of an animal was evidence of an acid reaction in that tissue. The first fact noted by DRESER that is of interest to us is that after a single dose of acid fuchsin the urine is found shortly thereafter to become brilliantly red. If the kidney from such an animal is examined no stained cells are noted anywhere in the kidney. To interpret this fact we would have to say that normally *the urine is acid in reaction, but the cells of the normal kidney are not.* The following may serve to corroborate this finding of DRESER:

EXPERIMENT 55.—Three frogs, weighing 35 grams each, are injected, respectively, with 0.25, 0.5, and 1.0 cc. of an aqueous 1 per cent acid fuchsin solution, into the dorsal lymph sac. All are seen to secrete a red-colored urine before being killed. They are killed respectively after 1, $1\frac{1}{2}$, and $4\frac{1}{2}$ hours. On autopsy, *red urine is found in the bladder of each animal. The kidneys are not stained.* They are rapidly removed from the freshly killed animals, frozen with liquid carbon dioxid (on a BARDEEN freezing microtome, where the gas does not come in contact with the tissue) and sectioned. The sections are immediately transferred to a slide (without being brought in contact with water or any other medium except air), covered with a cover slip, and examined under the microscope. *None of the kidney tissues is seen to be stained.* To be sure that the freezing plays no part in the findings, a parallel series of free-hand sections and crush preparations of the kidneys are made. No stained cells are found.

When the uncolored sections are touched with very dilute acetic acid they are seen gradually to assume a pink color. *Acid fuchsin is therefore present in the kidney tissues,* but as cut from the body the reaction of this organ is not such as to allow its red color to appear. The pink tinge visible in the kidney after being touched with acid *includes the glomeruli.*

EXPERIMENT 56.—To show that what was said for the frog holds also for the mammal, two young rabbits, weighing, respectively, 184 and 189 grams, received into the ear veins 2 and 4 cc., respectively, of a 1 per cent aqueous acid fuchsin solution. At the end of thirty and thirty-five minutes, respectively, they were killed by a blow on the head and immediately autopsied. Light red urine was found in the bladder of the first, deep red urine in that of the second. The appearance of the kidneys in both animals was entirely normal, and no dye was visible in the kidneys either macroscopically or microscopically. When a little very dilute acetic acid was permitted to flow under the cover slips, the sections turned uniformly pink.

DRESER noted no staining of the frog's kidney until he had repeated his acid fuchsin injections several times. Then he

found that the cells of the convoluted and of the straight tubules began to stain red. He interpreted this finding by saying that from the long-continued effort on the part of these cells to excrete the dye, they become fatigued and so some of the dye remains behind to be discovered on subsequent section of the kidney. From all these facts DRESER concluded that the acid constituents of the normal urine are "secreted" by the convoluted tubules, and that since the glomeruli and their capsules remain unstained, the "urine" coming from these must be "alkaline" in reaction, to change to an acid reaction after passing by the convoluted tubules. Whether such conclusions are really justified we shall have occasion to discuss later.

No one can quarrel with the simple experimental finding that acid fuchsin does not stain the normal kidney, and does do this after repeated and long-continued injections. Such staining of the kidney DRESER still regards as "physiological." Strictly speaking, and for reasons that will be apparent as we go on, I shall myself regard it as "pathological." What DRESER calls *the "fatigue" of the cells of those portions of the kidney which stain after repeated injections of the acid fuchsin, we are perfectly safe in regarding as the first evidences of an abnormal acid content in these cells, and we may hold that the repeated injection of this dye is itself responsible for such a condition.*

Acid fuchsin is a weak acid, and must produce the same effects upon the kidney that we know are produced by the injection of any other acid.[1] After the injection of acids we note regularly all the signs of a nephritis, and that these were not absent in DRESER's experiments is clearly evidenced by the "anuria" which this author so often noted in his frogs.

But DRESER[2] describes yet another experiment which shows that an abnormal production or storage of acid occurs in the kidney in nephritis. The kidney of the frog receives a blood supply, it will be remembered, from two sources—through the renal artery, as in mammals, and through a sort of portal system analogous to that existing in the liver. The blood from both these sources mixes to leave the kidney by way of the renal vein. DRESER *noted that if acid fuchsin is injected into the abdominal vein an hour after the renal artery has been tied, the convoluted*

[1] See page 489.

[2] H. DRESER: Zeitschr. f. Biol., **21**, 53 (1885).

tubules stain red. As already pointed out, no such red staining of the cells is noted if the dye is so injected without ligation of the renal artery. DRESER interprets his finding in the terms of physiology, but that we deal here with a pathological condition of the kidney—a nephritis—is betrayed not only by the fact noted by DRESER, that kidneys so treated secrete no urine, but by the evidence furnished below,[1] that after occlusion of the arterial blood supply to the kidney, acid develops in this organ, the kidney swells, the water secretion falls and casts and albumin appear in the urine.

Further tinctorial evidence of an abnormal production or accumulation of acid in the kidney in nephritis is furnished by certain experiments of R. HEIDENHAIN, M. NUSSBAUM and P. GRÜTZNER with sodium indigosulphonate. This dye behaves similarly to acid fuchsin. It is deep blue or indigo in an acid solution and yellow in an alkaline one. The somewhat contradictory conclusions of these authors, based on their studies with this dye, are easily put in order if we try to separate those of their findings which are pathological from the physiological. In my own experiments on rabbits and frogs, I have, first of all, never been able to confirm any but the conclusion of NUSSBAUM,[2] that *no part of the normal kidney stains with sodium indigosulphonate.* This corroborates the finding obtained with acid fuchsin—*the normal kidney does not contain sufficient acid to bring out the blue color.*

EXPERIMENT 57.—Four frogs, weighing 30 grams each, are injected respectively, with 0.25, 0.5, 1.0, and 0.25 cc. of a 1 per cent aqueous sodium indigosulphonate solution into the dorsal lymph sac. Blue urine is voided by each of the animals before being killed. After, respectively, forty minutes, fifty minutes, seventy minutes, and 3½ hours, their heads are cut off and they are autopsied. Blue urine is found in the bladders of the last three. Macroscopic examination shows *no color anywhere in the kidneys of these animals,* and microscopic examination of frozen sections only confirms this fact.

EXPERIMENT 58.—Three rabbits from the same litter, and weighing 497, 575, and 447 grams, respectively, receive, respectively, through the ear vein, 1, 2, and 5 cc. of a 1 per cent aqueous sodium indigosulphonate solution. They are killed by a blow on the head one hour after being injected. Blue urine is found in the bladder of each. This

[1] See pages 267, 498 and 659.

[2] M. NUSSBAUM: Pflüger's Arch., 16, 141 (1878).

is also present in the ureter of the third. *The kidneys are entirely unstained* in the first two, and no color is found anywhere in the frozen sections prepared from these kidneys. The kidney of the third animal has a mottled blue appearance superficially, and one section shows some blue streaks radiating toward the pelvis of the kidney. *Frozen sections show no dye anywhere in the kidney substance proper.* The blue streaks are due to dye found in the *lumina* of a few of the collecting tubules.

In apparent contradiction to this simple conclusion that the normal kidney does not stain with sodium indigosulphonate, stand the classical experiments of HEIDENHAIN,[1] who found certain portions of the kidney, notably, again, the convoluted tubules, to stain when the "secretion of the urine was sufficiently depressed." HEIDENHAIN brought about the desired reduction in the secretion of urine by such procedures as transverse section of the spinal cord in the neck. But as he himself noted, this produces an enormous fall in blood pressure. Such a fall does not, however, leave the kidney in a normal condition—it spells not alone an anuria, but an albuminuria and casts, in other words, a "nephritis." *The staining of the kidney under these circumstances is again evidence of an abnormal production or accumulation of acid in this organ,* a conclusion that we shall shortly be able to corroborate by entirely different methods.

Both HEIDENHAIN and DRESER have laid special stress on the fact that the convoluted tubules stain under the conditions offered in their experiments, while the glomeruli remain unstained, because it is upon this fact chiefly that they (and their followers) have based their conclusion that the different parts of the uriniferous tubule in its course from the glomerulus to the pelvis of the kidney have different functions. As generally held, these different parts are supposed to secrete into (or, according to CARL LUDWIG, absorb from) the mother urine—the liquor postulated by W. BOWMAN to be separated from the blood in its passage through the glomeruli—as this flows down the uriniferous tubules, the different substances which serve to characterize the urine. I do not myself question the probability that the different portions of the uriniferous tubules have different functions, but that this is so is not proved by these particular experiments. Strictly speaking, the findings of DRESER and HEIDENHAIN only show

[1] R. HEIDENHAIN: Pflüger's Arch., **9**, 1 (1875); Hermann's Handbuch d. Physiol., **5**, 346, Leipzig (1883).

that, *under the conditions of their experiments, the neutrality mechanism existing in the convoluted tubules is broken down more easily than that existing, for example, in the glomeruli.* That this approximates more nearly a correct interpretation of the observed phenomena is, as a matter of fact, indicated by the following:

By simply continuing the conditions which were mentioned as effective in leading to a staining of the convoluted tubules, we get a staining of the glomeruli. Evidence for the correctness of this conclusion can be adduced even from some cursory experiments mentioned by HEIDENHAIN and GRÜTZNER. As pointed out above, the conditions which lead to a staining of certain portions of the kidney with acid fuchsin or sodium indigosulphonate (excessive acid injection, ligation of renal artery, gross falls in blood pressure) are conditions which we can show by other means to be such as are associated with an abnormal production or accumulation of acid in the kidney. No matter how we interfere with a proper blood supply to the kidney we get such a production of acid. It does not, therefore, surprise us that when GRÜTZNER [1] produced circulatory disturbances in the kidney by injecting gum arabic, he noted not only the development of anuria and albuminuria, but found at the same time that the glomeruli and their capsules now stained with sodium indigosulphonate. Quite as simply can we interpret HEIDENHAIN'S [2] finding that the glomerular tufts stain with sodium indigosulphonate when the ureters are ligated. When this is done the urine is dammed back and accumulates in the space between the glomerular tuft and the parietal layer of the capsule, in consequence of which the capillaries composing the tuft are compressed, so that the normal circulation of blood cannot now occur through them. Under these circumstances an abnormal production or accumulation of acid in the cells of the glomerulus and the capsule is rendered possible and so the tissues making up these structures now stain.

One can further test the soundness of the reasoning detailed here that a staining of the kidney as a whole or in part marks the presence of an abnormally high acid content by working with excised kidney. Slices of fresh kidney kept in dilute solu-

[1] P. GRÜTZNER: Pflüger's Arch., **24**, 461 (1882).

[2] R. HEIDENHAIN: Hermann's Handbuch d. Physiol., **5**, 372, Leipzig, (1883).

tions of sodium indigosulphonate or acid fuchsin stain only very slowly and very slightly. But let a trace of acid be added and *all* parts of the section may be made to stain a deep blue in a few minutes. In the same way a section of tissue from a kidney that has been dead some time (and so contains postmortem acids) stains readily, and, let it be noted, in all its parts.

It will be recalled by anyone familiar with such studies as those of HEIDENHAIN, DRESER or the numerous investigators who since their day have adopted similar experimental methods, that these studies are intended to throw light on the problem of secretion by the kidney cells. This process of secretion is, of course, a dynamic one, made up of two parts, the one concerned with the taking up from the blood of the substance to be secreted, the other with the giving off of this same substance in the urine. The problems involved here are discussed in detail later, but it may not be amiss to point out even now that what is so often done, namely, the regarding of a mere staining of some or all of the cells of an organ as dependable evidence indicating that the dye is " secreted " by these cells, is entirely wrong. The presence of a dye in a cell does not mean this; nor when cells stain unequally does it mean that those most deeply stained are most involved in this process. *It may mean just the reverse.* The staining of the excised kidneys described above shows this very clearly. A kidney touched with a little acid, or one showing postmortem change, stains better than a normal kidney, and this without any hope of subsequently " secreting " the absorbed dye. Again, a kidney rendered " nephritic " by ligation of its arterial blood supply stains better than a normal one, and yet no one would maintain that a nephritic kidney " secretes " all dissolved substances better than a healthy one.

What really happens in the excised kidneys, or in the " nephritic " kidneys contained in the still living animal, represents but an isolated expression of the general laws that we to-day know to underlie all that is comprised in the physical chemistry of the process of dyeing. *The kidney cells in the experiments that have been detailed are stained for the same reason, and their staining reactions mean the same thing, as when any ordinary lyophilic colloid such as fibrin or gelatin takes up acid fuchsin or sodium indigosulphonate.* If these colloids are seen to be stained red or blue, it means that they contain, under the conditions of

the experiment, a certain minimum of acid. But with a given concentration of the dye the depth of the staining becomes a measure of the acid content, for a given colloid will absorb the more of any so-called "acid stain" the higher the concentration of the acid in the colloid. Other things being equal, the kidney cells must stain the more intensely with acid fuchsin or sodium indigosulphonate, the higher the acid concentration developed in them. To this whole question we shall have to return later.

§ 5

Yet other lines of evidence may be adduced to prove that in nephritis there is an abnormal production or accumulation of acid in the kidney. To some of these we return later.[1]

When the carnivorous animal (including man) is subjected to intoxication with acid, it meets this to begin with, by neutralizing the acid with the fixed bases of its body. But when these are heavily drawn upon the organism has a reserve mechanism which enables it still further to tolerate an acid intoxication—it converts an increasing amount of its protein material into ammonia and uses this to neutralize the acid. *The high relative and absolute ammonia excretion so common in many of the nephritides or in patients likely to show albumin and casts in the urine with a diminished water output*, as in starvation, after the anesthesias, after poisoning with phosphorus, arsenic, lead, etc., *becomes evidence, therefore, of the existence of abnormally great amounts of acid in them.* (Münzer, Palma, Araki, Badt, Laub, etc.)

The low carbonic acid content of their blood is further proof in the same direction.[2] When any of the fixed acids are introduced into the body, or are produced there (lactic, diacetic, betaoxybutyric, abnormally large amounts of sulphuric, phosphoric, etc.), either in the course of normal or deranged metabolism these tend to drive off the volatile carbonic acid from the blood exactly as in test-tube experiments. The low carbonic acid content of the blood so common in nephritis and in many of the

[1] See page 778.

[2] See H. Meyer: Arch. f. exp. Path. u. Pharm., **14**, 313 (1881); **17**, 304 (1883). See also Lewis, Ryffel, Wolf, Cotton, Evans and Barcroft: Heart, **5**, 45 (1913); Jour. Physiol., **46**, 53 (1913); Yandell Henderson: Jour. Am. Med. Assoc., **63**, 318 (1914).

intoxications accompanied by casts, albumin, etc., in the urine is explained in this way.

Quite recently interesting colloid-chemical evidence of an abnormal production or accumulation of acid in the body in nephritis has been brought by F. von Hoefft.[1] The coagulation temperature of proteins is reduced, their alcohol precipitability and electrical conductivity increased whenever their acid content is raised.[2] The blood of patients with nephritis shows all these changes.

The work of A. W. Sellards[3] on the tolerance of patients to administration of alkali (sodium bicarbonate) before they react to the point of secreting a neutral urine is also of interest here. While normal individuals require some 5 to 10 grams, patients with recognized "acidoses," produced by feeding acid or in diabetes, were found to need more than these amounts (30 grams) before their urines turned neutral. Sellards proposes the use of such alkali feeding by way of settling whether the "nephropathies" are due to "acidosis." Without questioning the justice of Sellards' classification of his patients—for as I have insisted it is most important to know whether all of a kidney is diseased or only pieces in it—he finds that five of his thirteen cases showed a normal tolerance while in all the rest it was increased. In one patient he did not get neutral urine even after injecting 60 grams of sodium bicarbonate intravenously, and in a second the urine was still acid after 130 grams. Sellards' work has frequently been quoted as evidence against my views, but if I am any judge, it is simply a way of saying backwards that there is evidence of an abnormal production or accumulation of acid in the body in nephritis.

III

ANY MEANS WHICH LEADS TO AN INCREASED PRODUCTION OR ACCUMULATION OF ACID IN THE KIDNEY IS A MEANS OF PRODUCING NEPHRITIS

We are now ready to discuss the converse of what has gone before, and so try to show that *any means by which we can bring*

[1] F. von Hoefft: Kolloid-Zeitschr., **13**, 278 (1913).

[2] See page 147.

[3] A. W. Sellards: Johns Hopkins Hosp. Bull., **23**, 289 (1912); ibid., **26**, 141 (1914).

about an abnormal production or accumulation of acid in the kidney constitutes a method of producing the signs of nephritis.

§ 1

The simplest way of increasing the acid content of the kidney consists, of course, in the *introduction into this organ of an acid* of some kind. This is done most easily by injecting the acid, either in solution in water or in a "physiological" salt solution, directly into the general circulation of an animal. For this purpose I used, in my own experiments, a large-sized aspirating syringe with a two-way valve, rubber tubing and a hypodermic needle, as illustrated in Fig. 143. The acid solution warmed to 37° C. is sucked into the syringe through the tube *a*. After turning the valve *v* it can be ejected, on lowering the plunger, through the tube *b*, which ends in the hypodermic needle *n*. The needle is inserted into the ear vein of a rabbit and is held in place by a couple of small artery forceps. As the acid is injected intravenously, one observes the normally alkaline urine of the rabbit to become neutral and then to turn acid, and as this acidity rises, albumin appears in the urine. The following experiments dealing with the effects of such intravenous acid injections will serve to illustrate this point. Let it be noted that in addition to the appearance of albumin in the urine, this comes to contain various casts, epithelial cells, blood corpuscles and hemoglobin. By

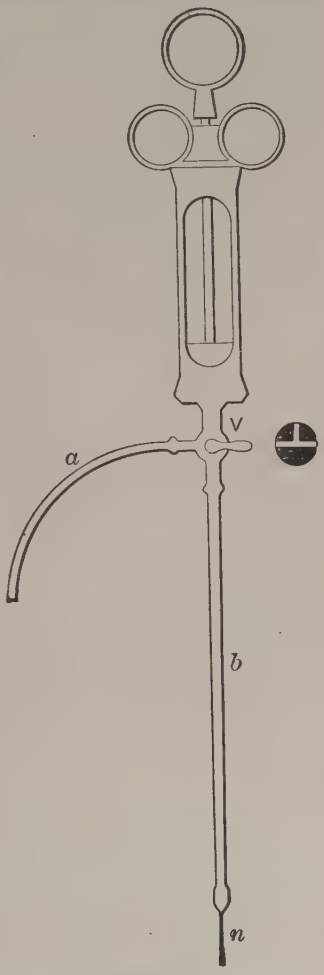


FIGURE 143.

comparing the urinary output in these animals with that shown by normal animals,[1] it is seen that this is decreased. Evidences of œdema are also not wanting; animals injected with an acid do not excrete the water that is injected with this acid as does a normal animal that is given water only, in the form of a "physiological" salt solution. The water when injected *with an acid* is retained in the body, but to this phase of the problem of nephritis we shall need to return later. For the present it is clear that *there develop all the most typical signs of an acute nephritis when acid in sufficient amount is injected into an animal.*

EXPERIMENT 59.—Belgian hare; weight 1870 grams. Has been fed corn, oats, hay, and cabbage. Urine obtained by gentle manual pressure over the bladder.[2] In the time of the experiment there are injected, at 37° C. and at a uniform rate, with the exceptions noted, 291 cc. of the following mixture: 300 cc. n/20 HCl+20 cc. 2/m NaCl.

Time.	Amount of urine in cc.	Remarks.
1.20	.....	Tied to animal board. No anesthetic.
1.45	4.0	Turbid, yellow, no albumin, no casts.
2.00	6.0	
		Injection into ear vein begun.
2.15	Few drops	Turbid, yellow, no albumin, no casts.
2.30	1.9	Clear, yellow, faint trace albumin, no casts.
2.45		
3.00	1.5	Clear, brownish tinge, albumin present, few red blood corpuscles, isolated kidney cells, no casts.
3.15	1.6	Smoky urine, albumin, isolated granular and epithelial casts.
3.30	1.3	
3.45	2.2	Smoky urine, albumin, isolated granular and epithelial casts. Injection interrupted for 2½ minutes.
4.00	4.8	Smoky urine, albumin, isolated granular and epithelial casts. Injection interrupted for five minutes.
4.15		Smoky urine, albumin, isolated granular and epithelial casts.
4.45	21.0	Hemoglobinuria. Injection interrupted for ten minutes.
5.00	.....	Animal dies.

[1] See pages 334 and 340.

[2] In these experiments on nephritis the *greatest care* is necessary not to injure the lower urinary passages and so get a bleeding which might, through the presence of albumin and blood in the urine, lead to the erroneous conclusion that a nephritis is at hand when only some bleeding is occurring into the bladder or urethra. Manual pressure over the bladder must be made with gentleness, and care must be taken not so to crowd the bladder into the pelvis as to kink the urethra. Only the smallest soft rubber catheter, well vaselined, must be introduced. If these precautions are not followed, fallacious, if not worthless, results are obtained. When an animal dies or is killed, the lower urinary passages must be examined for hemorrhagic points.

Total urine secreted since beginning injection **34.3** cc.

Autopsy.—Weight of animal 2135 grams! No free fluid in peritoneal, pericardial, or pleural cavities. Kidneys slightly bluish, and bleed freely on section. Nothing about them is strikingly abnormal.

EXPERIMENT 60.—Belgian hare; weight 2008 grams. Has been fed a mixed diet of corn, oats, hay, and cabbage. Urine obtained by gentle pressure over bladder. During the course of the experiment there are injected at 37° C., and at a uniform rate with the exception noted, 90 cc. of the following mixture: 90 cc. n/10 HCl +6 cc. 2/m NaCl.

Time.	Amount of urine in cc.	Remarks.
3.35	.....	Tied down. No anesthetic.
3.40	.....	Injection into ear vein begun.
3.55	6.0	Turbid, yellow, alkaline to litmus. No albumin, no casts.
4.05	1.7	Clearer, trace of albumin present.
4.20	0.8	Urine smoky, albumin increasing. Injection stopped for fifteen minutes as animal threatens to die.
4.40	.....	Injection recommenced.
4.45	Few drops	Bloody, much albumin, red blood corpuscles, great numbers of granular casts of various sizes.
4.47	.....	Animal dies.

Total urine secreted since commencing injection **8.5** cc.

Autopsy.—Weight 2078.5. No free fluid in the peritoneal, pleural, or pericardial cavities. Kidneys slightly swelled. Under the capsule appear tiny hemorrhagic points.

EXPERIMENT 61.—Belgian hare; weight 2259 grams. Diet unknown, as he has just been received in the laboratory. Urine obtained with a catheter. In the course of the experiment 75 cc. of the following solution are injected intravenously at a uniform rate, with the exception noted: 75 cc. n/10 HCl +5 cc. 2/m NaCl.

Time.	Amount of urine in cc.	Remarks.
11.30	7.0	Tied to animal board. Urine thick, chrome yellow, no albumin.
11.45	19.4	Thick, chrome yellow, no albumin, alkaline to litmus paper. Injection into vein of ear begun.
12.00	2.0	Thick, chrome yellow, no albumin, alkaline to litmus.
12.15	0.4	
12.30	1.6	Clearer, pinkish tinge, albumin present.
12.40	.....	Injection stopped entirely.
12.45	3.7	Urine distinctly red, much albumin, many casts.
1.45	11.5	Urine turbid, red, shows spectrum of oxyhemoglobin, filled with albumin, casts, (epithelial, granular and mixed), epithelial cells and red blood corpuscles. Animal released in good condition, returned to hutch.

Total urine secreted since beginning injection **19.2** cc.

5.30	5.0 per catheter.	Clear, yellow, acid. Casts and albumin still present.
11.00 Next morning	37.0 per catheter.	Dark amber, thick, faintly acid, clear. Microscopic examination shows many squamous epithelial cells and isolated casts. Carefully filtered urine shows a trace of albumin.

These nephritides produced experimentally in animals have a perfect parallel in the albuminurias with blood, casts, and a diminished urinary output to the point of cessation which are observed from time to time in human beings who have inhaled or swallowed by accident or intent sufficient quantities of various acids.

§ 2

It will be retorted by some that to inject acid intravenously is so " abnormal " that it and its consequent nephritis has nothing in common with the albuminurias and nephritides observed in human beings. To meet this criticism it is only necessary to examine the urine in conditions in which large amounts of acid are produced " physiologically " within the body itself. As is well known, large amounts of acid (especially lactic acid) are produced in the muscles when these contract. If the muscle works under physiological conditions and not too fast, the acid as formed may be largely oxidized *in situ*. But if the muscle works more rapidly then more acid is produced than can be oxidized in the muscles and so in the higher animals some passes unchanged into the blood, with this to the kidneys, and out in the urine.[1] It is evident that the opportunities for such an accumulation of acid in the body become the greater the more rapidly and the harder the musculature of the body works, and we should add, the more defective the oxygen supply to the working muscles, for this element is necessary for the proper oxidation of the acid in the body. Now such a combination of hard work with a (temporarily) defective oxygen supply to the active muscles is furnished whenever the organism engages in exercise that calls for more than usual effort. We are therefore

[1] Trasaburo Araki: Zeitschr. f. physiol. Chemie, **19**, 422 (1894), where references to his earlier papers may be found. Hoppe-Seyler: ibid., **19**, 476 (1894). Fletcher and Hopkins: Jour. Physiol., **35**, 247 (1907).

not surprised to find that soldiers after prolonged marches, women in labor, Marathon runners, etc., show albumin, casts, blood, etc., in the urine when examined after such exertions.[1] The amount of exercise needed to bring about such albuminurias is really surprisingly low, as is indicated by the following:

Experiment 62.—Seven trained athletes just before entering upon a game of basket ball were asked to void their urine into a series of flasks. At the end of the game, which lasted $1\frac{1}{2}$ hours, they voided their urine a second time into a second series of flasks. Heller's

Figure 144.

Figure 145.

test was then applied to the various specimens of urine. *While none of the players showed any trace of albumin in his urine before the play, all gave marked reactions after the game.* The results of the tests applied to the urines voided after the game are shown in Figs. 144 and 145. The first four tubes are photographed against a white background, the three of Fig. 145 against a black. The faint albumin ring present in the tube on the extreme right of Fig. 145 scarcely shows in the photograph. Interestingly enough, this specimen of urine came from a player who was in the game but five minutes.

Experiment 63.—Five trained athletes shortly before engaging in a match game of basket ball void their urine into a series of flasks.

[1] W. Leube: Virchow's Arch, **72**, 145 (1878). G. Edlefsen: Centralbt. f. d. med. Wissensch., 762 (1879). C. von Noorden: Arch. f. klin. Med., **38**, 205 (1886).

All the urine voided during the succeeding $1\frac{1}{2}$ hours during which the game is played is collected in a parallel series of flasks. In none of the control urines with the exception of that of Player IV are there found albumin or casts. This player had found it necessary before coming to the game to rush about town making train and street-car connections and had moreover had a "cold" for three days previously. After the game all the players showed an albuminuria and a great many granular, hyaline, and mixed casts. The albumin and the casts in the previously affected individual were markedly increased. The findings are illustrated in Fig. 146 and in the appended Table

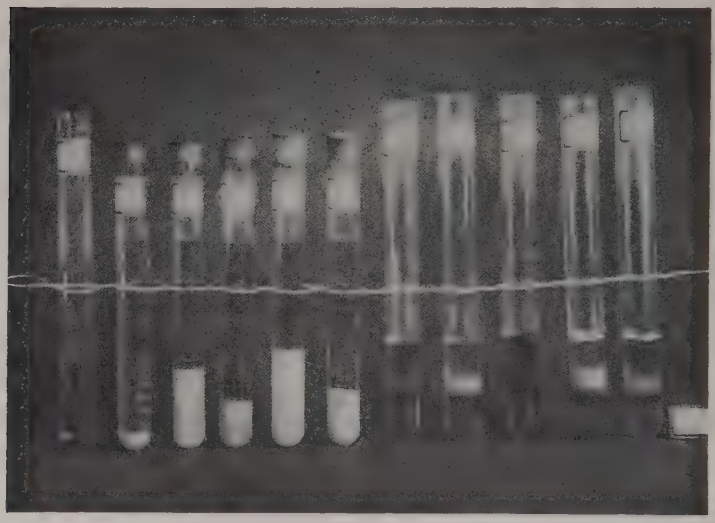


FIGURE 146.

CIV. The five tubes on the right show the results of applying the cold nitric acid test to the urine after the game. The tube on the extreme left shows the albuminuria existing in Player IV even before entering the game. The quantitative estimations in the ESBACH tubes were carried out in the ordinary way using TSUCHIYA's [1] phosphotungstic acid reagent. The photograph was made after the tubes had stood for only six hours. The readings in the table were made after twenty-four hours.

[1] TSUCHIYA: Centralbl. f. inn. Med., **29**, 105 (1908).
Phosphotungstic acid, 1.5 grams.
Concentrated hydrochloric acid, 5 cc.
Alcohol enough to make 100 cc.

TABLE CIV

BEFORE THE GAME

Player	Amount of urine in cc.	Nitric acid test.	Casts.
I	60	Negative	None
II	158	Negative	None
III	5	Negative	None
IV	47	Positive	Occasional granular and hyaline
V	134	Negative	None

AFTER THE GAME ($1\frac{1}{2}$ HOUR PERIOD).

Player.	Amount of urine in cc.	Nitric acid test.	Casts.	ESBACH reading with phospho-tungstic acid.	Albumin excreted in grams.
I	168	Positive in all	Many hyaline, granular and mixed casts present in all.	0.6	0.111
II	69			3.25	0.224
III	35			2.3	0.080
IV	30			5.0	0.150
V	94			2.75	0.258
					Av. 0 163

A remarkably short period of hard athletic work suffices to produce a great albuminuria, as the following taken from many such observations shows:

EXPERIMENT 64.—B——, a well-trained and expert University runner ran a quarter-mile race. Before starting he voided 54 cc. of urine which on examination showed no albumin. After his race (time: 58 seconds!) he voided 59 cc. of urine in which much albumin was found. In Fig. 147 are shown the results of the albumin tests as applied to the two samples of urine. In the two tubes on the right the cold nitric acid test has been applied to the urines; in the tube on the left a quantitative estimation has been carried out in an ESBACH tube with TSUCHIYA'S phospho-tungstic acid reagent.

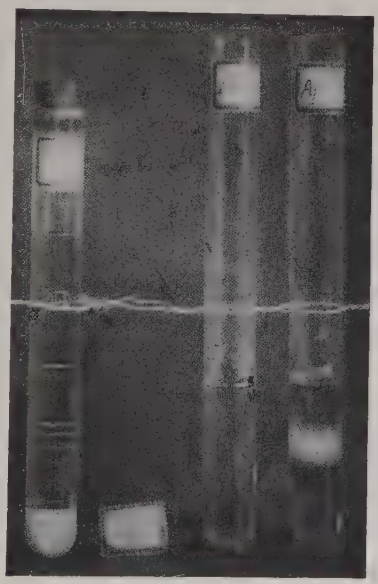


FIGURE 147.

§ 3

A condition in the body analogous to that produced voluntarily by the athlete in his athletic activities is created through any *uncompensated heart lesion or any disease of the lung* of such a character as to interfere materially with the proper aëration of the blood. Under these circumstances there is not produced the excessive amount of acid by extra muscular exertion, but the oxidation of such amounts as are normally present has been decreased by not permitting the normal amount of oxygen to get to the tissues of the body. The end result is, of course, the same. A defectively functioning heart or a sufficiently disabled lung interferes first of all with the proper escape of carbonic acid from the blood (and so from the cells in which this is produced).[1] But they do more than this, they place the organism as a whole in a state of lack of oxygen, and as a necessary consequence of this we know from the studies of Trasaburo Araki,[2] Hermann Zillessen,[3] and P. von Terray[4] that we get an abnormal production and accumulation of other acids, notably lactic and oxalic acids, in the tissues. Heart or lung lesions therefore are potent to lead to that same abnormally high acid content of the cells of the kidney that we previously found created through the direct injection of acids, or the hard work of the athlete, and so we are prepared to find in these pathological states of the heart and lung that albuminuria with casts, and a defective secretion of water is again a common consequence. As a matter of fact the association of "nephritis" or "Bright's disease" with heart lesions of the most varied kinds, or pathological conditions in the lung (manual compression of the thorax, pleurisy with effusion) that reduce its ventilation area sufficiently, is so constantly observed that it is taken for granted clinically.

[1] Strassburg: Pflüger's Arch., **6**, 94 (1873); A. Ewald: Arch. f. (Anat. und) Physiol., 663 (1873); 123 (1876).

[2] T. Araki: Zeitschr. f. physiol. Chemie, **15**, 335 and 546 (1891); **16**, 453 (1892); **17**, 311 (1893); **19**, 422 (1894).

[3] H. Zillessen: Zeitschr. f. physiol. Chemie, **15**, 387 (1891).

[4] P. von Terray: Pflüger's Arch., **65**, 393 (1896).

§ 4

It requires no special comment to recognize that a whole series of pathological states such as the severer anemias, carbon monoxid poisoning,[1] and epileptic seizures, which at first sight seem to have nothing in common with each other, contain within themselves all the elements necessary for the development of the signs of a nephritis. The severe anemias (leukemia or pernicious anemia) merely constitute further ways of interfering with a proper oxygen supply to the tissues. Both are accompanied by an abnormal storage and production of acid in the tissues as evidenced by FELIX HOPPE-SEYLER'S[2] and T. IRASAWA'S[3] chemical analyses of the urine, and R. VON JAKSCH'S[4] titrations of the blood in cases of severe anemia. An abnormal acid production in carbon monoxid poisoning has been proved by T. ARAKI,[5] E. MÜNZER and P. PALMA;[6] in epilepsy (severe muscular exertion with defective breathing) by ARAKI and E. MENDEL. As clinicians well know, the finding of albumin, casts, blood, etc , in the urine in any of these pathological states is usual.

§ 5

The etiological importance of "cold" (in the strict sense of the word as a lowering of the body temperature and unaccompanied by an infection) in the production of an acute nephritis, or in the lighting up of a chronic one that has slumbered for a time, has always been insisted upon by earlier observers. This view finds a rigid scientific support in our present knowledge of the physiological effects of low temperature upon the warm-blooded animals. Of these none is more characteristic than the rise in the acid content of the cells of an animal so exposed.[7]

[1] G. THOMPSON: Trans. Assoc. Am. Physicians (1902); WILLIAM RAVINE: Personal communication.

[2] F. HOPPE-SEYLER: Zeitschr. f. physiol. Chemie, **19**, 473 (1894).

[3] T. IRASAWA: Zeitschr. f. physiol. Chemie, **15**, 380 (1891).

[4] R. VON JAKSCH: Klinische Diagnostik, 5th Ed., 2, Berlin (1901).

[5] T. ARAKI: Zeitschr. f. physiol. Chemie, **15**, 335 (1891).

[6] E. MÜNZER and P. PALMA: Prager Zeitschr. f. Heilk., **15** (1894).

[7] See ARAKI: Zeitschr. f. physiol. Chemie, **16**, 453 (1892). On the basis of this same acid production we can with ease explain the precipitation of an attack of hemoglobinuria in the cases of so-called paroxysmal hemo-

How potent is this element of cold in leading to the signs of a nephritis has been well brought out by R. D. KENNEDY,[1] who in Northern Michigan (Calumet) during extremely cold weather found albumin in 40 per cent of all patients examined who had been exposed to it. Thirteen of fourteen physicians in the hospital had albumin and casts in their urines some time through the winter. The only exception was an eye specialist who worked indoors. But even more trivial exposures to cold suffice to bring about these consequences. A cold bath, for example, leads, in not a few individuals, to the appearance of albumin in the urine.

§ 6

Thus far we have discussed only general conditions—conditions affecting the whole animal—that are capable of inducing an abnormal storage or production of acid in the body, and so of inducing a nephritis. We shall now consider a series of more local conditions that bring about the same result.

Instead of interfering with the normal action of the heart or lungs an effective state of lack of oxygen in the kidney can, of course, be induced by direct interference with the normal blood flow through this organ. Experimentally such a condition is easily established by total or partial ligation of either the arterial or the venous blood supply of this organ, a state that has its clinical parallel in such affections as partial or complete occlusion of the renal vessels through arteriosclerosis, thrombosis, embolism or the pres-

globinuria when these patients take a cold bath, are exposed to cold, etc. The acid produced under these circumstances rises to the point where it leads to hemolysis of the patient's red blood corpuscles. This view is supported by the fact that it is possible to precipitate an attack of hemoglobinuria for diagnostic purposes quite as easily through temporary obstruction of the circulation in the arm by applying a band about it (accumulation of carbonic acid and production of other acids due to a lack of oxygen) as through the customary immersion of the extremities in cold water. The essential nature of the paroxysmal hemoglobinurias would seem to reside in the lesser resistance which the red blood corpuscles of such patients have to such a hemolytic agent as an acid. The resistance is enormously increased by the addition of various salts to the blood, as OSCAR BERGHAUSEN has shown. This fact is not only of theoretical interest, as I have tried to show in discussing the nature of hemolysis (see page 438 or FISCHER: Kolloid-Zeitschr., 5, 146 (1909)) but of practical use in the treatment of these cases of hemoglobinuria which need a diet rich in alkalies, calcium salts, etc.

[1] R. D. KENNEDY: Personal communication (1912).

sure of tumors, etc., upon these vessels. But as the experiments of T. Araki and H. Zillessen have shown, such an interference with the normal blood supply (oxygen supply) to any of the parenchymatous organs is followed immediately by the accumulation of acids in the affected tissues. Do we find that in such local circulatory disturbances of the kidney we get an albuminuria? That we do is, of course, known to everyone—it constitutes, since Max Herrmann's [1] experimental studies, one of the classical facts of pathological physiology; it is attested to by the experience of the medical diagnostician; it is the bugbear of surgeons who operate on the kidney and find a temporary closure of the renal vessels expedient or necessary.[2]

§ 7

Instead of interfering directly with the oxygen supply to the kidney by procedures which interfere with the blood supply to this organ, we can bring about the same result in a more subtle way by giving the kidney parenchyma its normal oxygen supply, but by so interfering with the chemistry (enzymotic processes) of the cells themselves that make up the kidney as to render these incapable of utilizing in proper form the oxygen that is freely supplied them. So far as the end result is concerned, it matters little, of course, whether we interfere with the normal oxidation, say, of the carbohydrates of the living cell to carbonic acid by shutting off the oxygen supply to the cell and so halting the decomposition of the carbohydrates when these have been changed to lactic, oxalic, formic and other acids (saccharinic acids); [3] or whether we do nothing about the oxygen supply but

[1] Max Herrmann: Sitzungsber. d. Wiener Acad., math.-phys. Klasse, **65** (1861).

[2] For a discussion of the methods to be employed in combating the evil consequences of such temporary closure see the section dealing with the treatment of nephritis.

[3] The chemical aspects of this problem of the formation of acids from carbohydrates in the absence of oxygen are discussed by Felix Hoppe-Seyler: Berichte d. deut. chem. Gesellsch., **4**, 346 (1871); H. Kiliani: ibid., **15**, 701 (1882); Duclaux: Compt. rend., **94**, 169; Schützenberger: ibid., **76**, 470; Buchner, Meisenheimer, and Schade: Berichte d. deut. chem. Gesellsch., **39**, 4217 (1906); J. U. Nef: Liebig's Annalen, **357**, 214 (1907). The biochemical aspects of this same problem are discussed in the papers on lack of oxygen already referred to on pages 235 and 273.

introduce something into the cell which prevents the oxidation of the lactic acid as formed (or more probably its mother substance, glycerin aldehyd) to carbonic acid.[1] The cells of the living body in the end get into the same state whether they have their oxygen supply cut off or whether this is not interfered with, but they are " poisoned " in such a way as to be unable to utilize this oxygen as normally.

As has been shown particularly well by T. Araki, a large number of poisons lead to the same state of lack of oxygen, with its associated abnormal production and accumulation of acids in the tissues, as do the grosser interferences with the oxygen supply to the various organs or the body as a whole, that have already been described. And so it cannot surprise us to discover that Araki's *list of poisons—poisons utilized to show that an abnormal acid production is the constant accompaniment of a state of lack of oxygen in the tissues no matter how produced—is identical with the list of poisons familiar to any laboratory or clinical worker who has busied himself with the problem of the toxic nephritides:* metallic salts, such as those of arsenic, uranium, chromium and lead; alkaloids, such as morphin, cocain, veratrin and strychnin; anesthetics, such as alcohol, acetone, ether and chloroform; unclassified poisons, such as amyl nitrite, the cyanids and phosphorus.

§ 8

In concluding this section we need to discuss the albuminurias encountered in three conditions which not only are readily interpretable on the basis of our contention that albuminuria results whenever abnormally great amounts of acid accumulate in the kidney, but give this contention valuable support.

Since Rudolph Virchow's description of the condition fifty years ago, the *albuminuria of the newborn* constitutes a matter of common knowledge to every pediatrist. It occurs in perfectly healthy infants as a transitory phenomenon, is regarded as " physiological," and to it ordinarily no clinical importance is attached. Whence comes it? The condition is most commonly found in " hard " labors, when the cord prolapses, in breech presentations, etc., all of them conditions which mean a state of more than the

[1] In this connection see the interesting work of R. T. Woodyatt: Jour. Am. Med. Assoc. **55**, 2109 (1910).

normal lack of oxygen in the organism of the child during the process of its birth. Even normal labor means, of course, a decided interference with the circulation of the infant—is it not in this fact and the associated accumulation of carbonic acid and other acids in the blood that the cause of the first respiration is to be sought, as ZUNTZ has shown? Difficult labors mean *in toto* only a more than usual interference with the circulation of the child. It is entirely a matter of definition as to just how much of this we will accept as "physiological." But when we have thus connected the development of the albuminuria with a disturbance in the general circulation of the child then we have made it, at the same time, a mere subheading of the albuminurias discussed in § 3 of this section (page 496), and the albuminuria is "physiological" only as we will accept little or great interference with the circulation in the infant during its birth as "physiological."

Albuminuria is a common *accompaniment of salt starvation*, be this a complete salt starvation or only such a partial one as is induced by eliminating completely the sodium chlorid from the food. Under this same heading is to be classed the albuminuria consequent upon the *excessive consumption of water* low in salts. The latter washes the salts out of the body [1] and so leads indirectly to the same state as that induced by a lack of salts in the diet. The effect of a salt-free diet is twofold. In the first place it leads to the accumulation of acids in the tissues.[2] Other things being equal, we have on this basis alone therefore a reason for the appearance of the urinary findings characteristic of nephritis when salts are withheld from the diet. But the salts act in yet another way. As already discussed, and as we shall see in greater detail later, many of the changes induced in colloids by acid may be greatly inhibited through the presence of all salts, even neutral salts incapable of an effect that might be construed as due to a mere neutralization of the acid. Through the withdrawal of salts from the tissues, whether by salt starvation or through leaching these out with water, we favor, therefore, the development of the signs of a nephritis in two ways: not only do we render possible an abnormal production or accumulation of

[1] See page 368.

[2] G. BUNGE: Zeitschr. f. Biol., **10**, 111 (1874); see also J. FORSTER: ibid., **9**, 297, 369 (1873); N. LUNIN: Zeitschr. f. physiol. Chemie, **5**, 31 (1881).

acids in the tissues, but we take away at the same time the action of the salts in reducing the effect of the acids.

IV

NEPHRITIS DUE TO OTHER THAN ACID CAUSES

The colloid changes in the kidney which are characteristic of nephritis and which we shall discuss in greater detail later, such, for example, as the swelling of the kidney, are inducible, as previously noted, by other substances besides acids. Any agency thus capable of increasing the hydration capacity of a protein colloid and under physiological or pathological circumstances conceivably active in a kidney may in this way become a cause of the nephritic signs. Of the various ones which might be mentioned (alkalies, urea, pyridin, certain amins) and touched upon in the discussion of œdema, we shall here consider only the first, namely, the alkalies, in illustration of this point.

It so happens that the sum total of the chemical changes that go on in the living animal organism are of such a character as to threaten it chiefly from the acid side. Even under normal conditions, the tissues have to guard themselves against becoming acid. Is not carbonic acid among the chief end products of the oxidation of our foodstuffs? The normal tendency of the tissues to run over to the acid side is enormously increased under various pathological conditions, and as we shall find these conditions to be just such as are likely to lead to a nephritis, the discussion of this subject will naturally claim our chief attention. An abnormally high *alkali* content in the cells under ordinary circumstances is scarcely possible, and when it is induced artificially it is difficult to maintain, for the normal acid production (carbonic acid production) in the living cell tends quickly to neutralize it. This question is, therefore, scarcely to be considered in our further analysis of the problem of nephritis. Still, from a theoretical standpoint and in poison cases it is quite as important as that upon which we shall lay the greater stress. *We should, on the basis of our colloid conceptions of nephritis, be able to induce this condition experimentally quite as easily through alkalies as through acids.* As the following experiments show, this is actually the case.

EXPERIMENT 65.—Belgian hare; weight 2085 grams. Has been fed hay, oats, corn and cabbage. In the course of the experiment there are injected intravenously at a uniform rate 125 cc. of the following mixture: 150 cc. n/10 NaOH+10 cc. 2/m NaCl.

Time.	Amount of urine in cc.	Remarks.
2.35	31.0	Catheterized. Dark amber, acid to litmus paper. No albumin. No casts.
3.15	0.7	Weighed. Placed in animal board. Injection into ear begun. No albumin. No casts. Acid in reaction.
3.30	1.2	Urine clearer. Acid in reaction (?) Trace of albumin (?).
3.45	8.4	Milky, alkaline to litmus. Faint trace of albumin.
4.00	6.0	Milky, alkaline to litmus. Isolated casts. Faint trace of albumin.
4.15	1.2	Milky, alkaline to litmus. More albumin. Many long hyaline casts with coarsely granular material sticking to them.
4.30	0.7	Milky, alkaline to litmus. Much albumin. Filled with casts.
4.45	0.4	Filled with casts. Bloody tinge to urine.
4.58	0.4+	Milky, alkaline to litmus. Much albumin. Filled with casts. Bloody tinge to urine. Animal dies.
	0.6 contained in catheter.	1.0 gram of feces lost. It is noted that the albumin reactions as obtained with cold nitric acid applied to the filtered acidified urine are not as intense as in the albuminurias induced by acid injections. (Less albumin?).

Total urine since beginning injection **18.9** cc.

Autopsy.—Weight 2187 grams! No fluid in the cavities. Intestinal contents seem somewhat more fluid than usual. Kidneys are firm, apparently somewhat swelled, and do not bleed easily.

EXPERIMENT 66.—White rabbit; weight 1911 grams. Fed hay, oats, corn, and greens. In the course of the experiment there are injected at a uniform rate 185 cc. of the following mixture: 225 cc. n/10 NaOH+15 cc. 2/m NaCl.

Time.	Amount of urine in cc.	Remarks.
2.15	85.0	Catheterized. Turbid, dark amber, acid. No albumin, no casts.
2.30	0.7	Turbid, dark amber, acid. No albumin, no casts.
2.45	0.7	Weighed. Injection into ear vein begun. Urine as before.
3.00	0.2	Urine as before.
3.15	1.0	Neutral to litmus. Clearer. Small amount of albumin. Many hyaline casts. Some have coarse granules in them.
3.30	6.4	Urine clear as water. Some albumin. Many hyaline casts. Some have coarse granules in them.
3.45	15.5	Urine clear as water. Only a few casts can be found. Albumin present.
4.00	22.0	Weakly alkaline. Albumin present. Isolated casts only can be found.
4.15	24.5	Albumin present. No casts can be found. The urine has a pink tinge (hemoglobinuria). No red blood corpuscles microscopically.
4.25	.....	Injection stopped.
4.30	23.0	Faintly alkaline. Clear, pink, no casts, no red blood corpuscles. Albumin present. Animal released. Seems entirely normal, and eats at once.

Total urine since beginning injection, **92.6** cc.

Weight 2000 grams!

EXPERIMENT 67.—White rabbit: weight 2177 grams. Fed hay, oats, corn, and cabbage. In the course of the experiment there are injected at a uniform rate 240 cc. of the following mixture: 225 cc. n/20 NaOH+15 cc. 2/m NaCl. Injection made into ear vein.

Time.	Amount of urine in cc.	Remarks.
1.50	10.0	Catheterized. Turbid, yellow urine. No albumin. No casts.
2.00	.....	Weighed.
2.15	1 drop	No albumin. Injection begun.
2.30	——	
2.45	0.2	Albumin present. Filled with casts, mainly hyaline in character, but some are finely granular. Much squamous epilium and cell detritus.
3.00	0.5	Alkaline to litmus. Albumin and casts as before, but all the casts are hyaline except for coarse, granular material contained in or attached to some.
3.15	0.2	Strongly alkaline. Albumin and casts as before.
3.30	2 drops	Strongly alkaline. Albumin and casts as before. The urine has a pinkish tinge (hemoglobinuria).
3.45	1.0	Strongly alkaline. Albumin and casts as before. Urine pinkish (hemoglobinuria). Red blood corpuscles are found and two microscopic blood coagula. This bleeding is attributed to traumatism (animal struggled and whipped catheter about).
4.00	2.8	Urine strongly alkaline. The animal has begun to shiver (acid production!) during the last fifteen minutes. The previously warm ears are pale and cold.
4.15	13.0	The urine becomes faintly alkaline, then scarcely affects either red or blue litmus. The urine is clear like water except for a clouding due to (traumatic) blood. Careful search of the sedimented urine reveals only an occasional cast. The animal is shivering constantly. It is killed.
4.30	12.0	
4.45	16.0	
5.00	19.0	
5.15	23.0	

Total urine since beginning injection, **87.7** cc.

Autopsy.—Weight 2326 grams! The peritoneal, pleural, and pericardial cavities are dry. The kidneys are soft and bleed a normal amount. A few pinpoint hemorrhagic spots are found in the bladder.

V

THE ALBUMINURIA

1. Introductory Remarks

Having discussed the evidence which shows that an abnormal production or accumulation of acid (alkali, pyridin, urea, amins) occurs in the kidney in every case of nephritis, and, conversely, that whenever such is brought about, the signs of nephritis become manifest, we need now to say how such a single factor is able to produce the various objective signs which as clinicians we have come to regard as characteristic of this pathological entity. The first to be considered is the albuminuria.

The urine of man or of the various animals that serve us for experimental purposes does not under normal circumstances contain albumin in an amount that betrays itself when any of our ordinary laboratory tests are applied to it. By special methods it is possible to show that even such normal urine contains faint traces of albumin, but it is generally held that this is of no pathological significance and has behind it a no more serious cause (it is thought) than the shedding and destruction of a few cells from the tract through which the urine has to pass from the uriniferous tubules into the outer world. An albuminuria, as we shall use the term, will, therefore, have a meaning only as applied to the presence of albumin beyond this normal amount, and, we ought to add, of renal origin and not from somewhere below this organ. Nor has the mechanism of the albuminuria which we are discussing anything in common with the albuminuria consequent upon gross destructive lesions in the kidney as when small or large blood vessels are ruptured, allowing their entire contents to escape into the urine.

Our current hypotheses regarding the cause of albuminuria are familiar to everyone and are notoriously unsatisfactory. It is generally held that the (chief) albumin of albuminuria is serum albumin, that it is derived from the blood, and that it is under normal circumstances prevented from going over into the urine by the kidney structures which lie between the urine and the blood. Some twenty years ago R. Heidenhain attempted to express the whole situation in satisfactory physico-chemical terms. He pointed out the colloid nature of the blood albumins, and called to mind Thomas Graham's fundamental differentiation between the colloids which do not diffuse through animal membranes and the crystalloids which do this readily. On this basis he maintained that the latter appeared in the urine because they could readily diffuse through the animal membrane that separates the urine from the blood, while albumin is absent because this colloid body cannot diffuse through such a membrane. We have not since Heidenhain's considerations gotten beyond this view.

Simple and apparently satisfactory as this explanation is, it cannot stand the pressure of a little analysis. In nephritis this membrane is, of course, still present, and yet in this pathological state the albumin appears in the urine. To meet this

fact it has been generally maintained, and, let us add, without any experimental support whatsoever, that the "permeability" of the urinary membrane for albumin has been altered, so that it now lets this through. As a matter of fact, we have not even had offered us any parallel from the pages of physical chemistry for such a change in the permeability of any "membrane" that in the laboratory corresponds with such as we might have in the body, nor, so far as I know, has anyone attempted to say just what chemical or physico-chemical agent is responsible for the changes in permeability postulated in the case of the kidney.

A first error in this theory of albuminuria (which represents the epitome of our present conceptions regarding its nature) *arises from the fact that the albumin found in the urine is looked upon as coming from the blood.* Such a belief has been entertained because it has been found that the albumin present in the urine shows a series of reactions which are identical with those obtained from serum albumin. But this does not yet prove that the albumin of albuminuria has come directly from the blood. Such a conclusion overlooks the important fact that the albumins contained in the kidney itself, in other words the albumins contained in the secreting membrane separating the urine from the blood, also show these reactions. None of the albumin reactions used in these tests is "specific." They only represent certain group reactions which colloid chemistry has shown us to be common to a large number of the protein colloids of animal origin. Such considerations carry with them the important conclusion that *the albumin of albuminuria need not come from the blood at all (except indirectly); it may come from the urinary membrane itself.* That, as a matter of fact, it does come from this will appear more distinctly as we proceed. *Albuminuria results whenever conditions are offered in the body which permit the solid colloid membrane that separates the blood from the urine to go into solution in the urine.* The chief reason why this occurs in nephritis resides in the fact that acids are produced which render the colloid membrane "soluble." To make clear what is meant by this conclusion we need but recall our previous remarks on the general structure of the kidney [1] and introduce some observations on this question of the "solubility" of colloids.

Many scattered but important facts regarding this problem

[1] See page 326.

are found in the literature of colloid chemistry, especially if we bear in mind that the "solution" of a protein is, in all probability, not a simple affair. We have learned how under the influence of an acid, the protein particles are hydrated and in increasing amount with increasing concentration. But under the same influence, as the "dissolved" state is approached, new properties are likely to be exhibited by the protein as indicated not only by a fall in its viscosity but by changes in its diffusibility, Brownian movement, susceptibility to precipitation, etc. *The protein moves from a state in which it is markedly colloid toward the crystalloid side.* Technically put, its degree of dispersion is increased.

An increase in swelling followed later by a decrease, an increase in viscosity giving way to a decrease, an increase in diffusibility, or in Brownian movement may all therefore be regarded as evidences for an increased "solubility." If this is borne in mind then THOMAS GRAHAM becomes one of the first students in this field, for he noted that the addition of acetic acid to egg albumin increased its diffusibility. On the other hand, E. VON REGÉCZY[1] found the addition of sodium chlorid to delay its diffusion.

Particularly important for our purposes are the studies of T. B. WOOD and W. B. HARDY,[2] who found plant protein (gluten) to maintain its "cohesiveness" (remain solid) in water and neutral media but to "disintegrate" and "dissolve" when a little acid was added. The solution in acid depended upon the nature and the concentration of the acid and was at all times inhibited by the addition of salts. While all salts (including sodium chlorid) showed this behavior some were relatively more powerful than others—the bivalent and trivalent radicals being more active, generally speaking, than the monovalent ones.

As previously emphasized, the urinary membrane (the kidney itself) is composed, in the main, of a mixture of hydrophilic protein colloids which, as we learned, are capable of existing in two fairly well-defined states: in a *solid or gel state* and in a *liquid or sol state.* A familiar illustration of such existence

[1] E. VON REGÉCZY: Pflüger's Arch., **34,** 431 (1884).

[2] T. B. WOOD and W. B. HARDY: Proc. Roy. Soc. London, Series B, **81,** 38 (1908).

in two states is offered by ordinary gelatin. Under certain conditions this appears in the form of a stiff jelly, under others as a "solution." In the same way fibrin represents the gel form of the sol fibrinogen, paracasein (casein) the gel of casein (caseinogen), ordinary soft rubber, the gel of a "dissolved" rubber, etc.

It is generally recognized that a rather close relationship exists between the gel state in which the colloid is "swelled" and the sol state of this same colloid in which it is "dissolved," and yet the transition from the one state into the other is not necessarily or in all examples a perfectly smooth affair. We need only to call attention to the fact that ordinary gelatin, for example, when thrown into cold water merely swells up—it enters the gel state. But in this state it remains, one might say almost indefinitely; to mere appearance it does not go into solution at all as would, for example, the crystals of any salt thus thrown into the solvent. But if the temperature of the water is raised then the gelatin goes into solution rapidly—it passes over into the sol state. A change in temperature in this case is necessary to accomplish its "solution." As to our mind albuminuria represents just such a passage of a colloid in the gel state (the proteins of the urinary membrane) over into a colloid in the sol state (the proteins contained in the urine of the albuminuric individual), let us study the conditions favoring such a transition in more detail, paying especial attention to such changes in surroundings as we might imagine could come into play in the cells of the living animal. Fibrin, gelatin and aleuronat [1] have been studied in this regard. The following facts regarding fibrin and gelatin are of importance in the further development of our subject.

2. Observations on the "Solution" of Colloid (Protein) Gels

(a) **Fibrin.**—When well-washed fibrin that has been thoroughly dried and then powdered in a mortar is thrown into water it swells up somewhat. Even though the vessel is thoroughly shaken *practically none of the protein goes into solution in the water.* The matter is easily tested by filtering the water off the fibrin and treating the filtrate in any of the accepted ways

[1] Marian O. Hooker and Martin H. Fischer: Kolloid-Zeitschr., **26**, 49 (1920).

for albumin. One must only be careful to use a fine filter or else not powder the fibrin so thoroughly that gross particles of it can pass through the pores. By similar means it can be shown that the *fibrin will not dissolve appreciably in any solution of the ordinary neutral salts. In a solution of any acid (or alkali) it not only swells up more than in water, but it goes into solution.* Within certain limits more and more fibrin goes into "solution" with every increase in the concentration of the acid (or the alkali). But in this matter there seems to exist an optimum above which the progressive increase in "solution" stops and gives way to a fall. There is, moreover, an upper limit to the total amount of fibrin that goes into solution in a given volume of the solvent. Under given conditions one has quite as much albumin in "solution" after shaking a mixture for two or three hours as after two or three days.

In a given concentration of acid (or alkali) the amount of fibrin that "dissolves" is markedly decreased through the addition of any neutral salt. With a progressive increase in the concentration of the salt there is a progressive decrease in the amount of fibrin dissolved. But the character of the salt is not immaterial. When equimolar solutions of different salts are compared, some act more powerfully than others, but on the basis of my experiments as thus far carried out it is unsafe to state definitely the order in which the various salt radicals affect the "solution" of the solid gel. The order seems to be identical with that in which they affect the swelling of fibrin. Monovalent radicals are, as a group, less powerful in decreasing the "solution" of fibrin in an acid (or an alkali) than are bivalent ones, and these than trivalent radicals.

What has been said will be rendered clearer by introducing a few typical experiments. Fig. 148 indicates the general way in which these experiments were performed. Weighed amounts of powdered fibrin were introduced into measured volumes of various solutions contained in Erlenmeyer flasks which were then placed in a shaking machine and shaken for various periods of time. At the expiration of this time the fibrin was allowed to settle, and the supernatant liquid was decanted off into a filter-lined funnel and received into a second flask. After stirring the filtrate, a measured volume was taken and the amount of "dissolved" albumin contained in it determined

quantitatively through precipitation with phosphotungstic acid [1] and measurement of the heights of the precipitate either in the graduated Esbach albuminometer tubes or calibrated test-tubes. As the experiments are purely comparative in character I have contented myself in these pages with simply photographing the results of a few of such as have a direct bearing upon our subject.

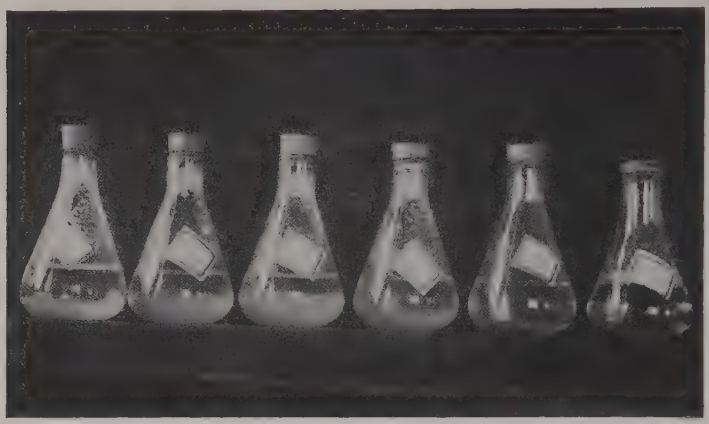


Figure 148.

Experiment 68.—0.5 gram of powdered fibrin was shaken up for five hours in each of the following solutions:

1. 50 cc. n/125 HCl
2. 50 cc. n/80 HCl
3. 50 cc. n/50 HCl.
4. 50 cc. n/25 HCl.
5. 50 cc. n/10 HCl.
6. 50 cc. H_2O.

The appearance of the fibrin in each of the flasks at the end of this time is shown in Fig. 148. In the first three flasks (1, 2, 3) there is progressive increase in the *swelling* of the fibrin with the progressive increase in the concentration of the acid. Beyond this point (flasks 4 and 5) there is a decrease in the swelling in spite of the further increase in the concentration of the acid. The least amount of swelling is noted in flask 6, which contains water only. The *solution* of the fibrin is indicated in Fig. 149. From left to right these tubes correspond with

[1] The phosphotungstic acid reagent had the following composition:

Phosphotungstic acid, 100 grams.
Sulphuric acid (sp.gr. 1.84), 100 grams.
Water enough to make 1000 cc.

the flasks of Fig. 148. No precipitate of albumin is seen in the tube on the extreme right, indicating that the fibrin did not go into solution appreciably in the water (neutral reaction). All the remaining tubes show a precipitate of albumin.

FIGURE 149.

EXPERIMENT 69.—0.5 gram of powdered fibrin was put into each of the following solutions and shaken for five hours:

1. 10 cc. n/10 HCl+40 cc. H_2O.
2. 10 cc. n/10 HCl+40 cc. m/8 NaCl.
3. 10 cc. n/10 HCl+40 cc. m/6 NaCl.
4. 10 cc. n/10 HCl+40 cc. m/4 NaCl.
5. 50 cc. H_2O.

The amount of albumin that went into solution is indicated in Fig. 150. No precipitate is seen in the tube on the extreme right (water). Most albumin is found in the first tube (pure acid solution). It is evident that the presence of the sodium chlorid reduces the amount of the albumin that goes into solution. The amount of this reduction is the greater the higher the concentration of the salt.

EXPERIMENT 70.—0.5 gram of powdered fibrin was placed in each of four flasks containing the following solutions and shaken for 5 hours:

1. 10 cc. n/10 HCl+40 cc. H_2O.
2. 10 cc. n/10 HCl+40 cc. m/8 Na_2SO_4.
3. 10 cc. n/10 HCl+40 cc. m/8 $MgSO_4$.
4. 10 cc. n/10 HCl+40 cc. m/8 $CuSO_4$.

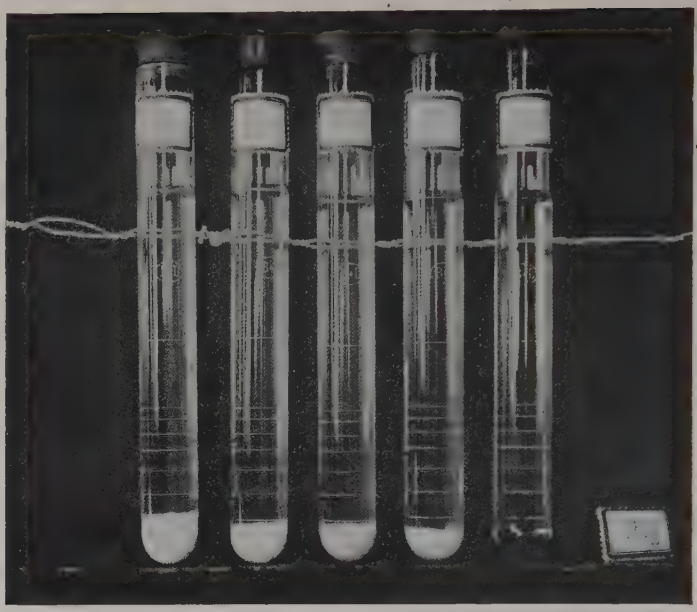


FIGURE 150.

FIGURE 151.

After filtering, the amount of albumin dissolved in the supernatant liquid found above the fibrin in each of the flasks was determined by mixing 20 cc. of filtrate with 14 cc. phosphotungstic acid. The result is shown in Fig. 151. As is readily apparent, each of the salts markedly reduced the amount of albumin that was dissolved.

FIGURE 152.

EXPERIMENT 71.—0.5 gram of powdered fibrin was introduced into each of five flasks containing the following solutions and shaken for five hours:

1. 10 cc. n/10 HCl+40 cc. m/8 sodium acetate.
2. 10 cc. n/10 HCl+40 cc. m/8 sodium nitrate.
3. 10 cc. n/10 HCl+40 cc. m/8 sodium sulphate.
4. 10 cc. n/10 HCl+40 cc. m/8 sodium citrate.
5. 10 cc. n/10 HCl+40 cc. H_2O.

The relative amounts of albumin found dissolved in each of these mixtures at the end of this time are indicated in Fig. 152. As is again evident, most albumin was dissolved by the pure acid solution. Each of the salts decreased through its presence the amount thus dissolved.

(b) **Gelatin.**—*What has been said regarding the "solution" of fibrin holds almost word for word for the "solution" of gelatin.* The best commercial gelatin shows some solubility in water. When, instead of being placed in water, gelatin is dropped into solutions of acids (or alkalies) this solubility of the

(commercial) gelatin is greatly increased. The presence of neutral salts in the acid (or alkali) solution decreases the amount of the gelatin that will go into solution. As in the case of fibrin, we note here again a progressive decrease in the amount that "dissolves" with every increase in the concentration of the added salt. With a given concentration the amount of such a decrease varies with the salt employed, and here again it seems that monovalent salt radicals do not as a group decrease the "solubility" of the gelatin as much as bivalent, or these as much as trivalent ones.

The following experiments may serve in illustration of what has been said:

Experiment 72.—The following solutions were prepared:

1. 100 cc. H_2O.
2. 100 cc. n/1000 HCl.
3. 100 cc. n/500 HCl.
4. 100 cc. n/200 HCl.
5. 100 cc. n/100 HCl.
6. 100 cc. n/75 HCl.
7. 100 cc. n/50 HCl.
8. 100 cc. n/40 HCl.
9. 100 cc. n/30 HCl.

Five leaves of dry gelatin, each measuring $3\frac{1}{2}$ by $1\frac{1}{2}$ cm., weighing altogether 0.5 gram, and obtained by cutting them out of the central portions of the large gelatin leaves that are obtained commercially, were dropped into each of these solutions. From time to time the dishes containing the solutions with their gelatin leaves were agitated so as to keep them from adhering to the sides, and aid the solution of the gelatin. All the vessels were treated exactly alike. The degree of solution of the gelatin after twenty-eight hours in these various solutions is indicated in Fig. 153. As the photograph shows, least gelatin is dissolved in the pure water. With the increase in the concentration of the acid there is a progressive increase in the amount of dissolved gelatin, but only up to a certain point, after which it falls in spite of the continued further increase in the concentration of the acid.

Experiment 73.—In the manner just described, 5 leaves of dry gelatin, weighing *in toto* 0.5 gram, and of the same surface were placed in each of the following solutions:

1. 100 cc. H_2O.
2. 15 cc. n/10 HCl+85 cc. H_2O.
3. 15 cc. n/10 HCl+$2\frac{1}{2}$ cc. 2/m NaCl+$82\frac{1}{2}$ cc. H_2O.
4. 15 cc. n/10 HCl+ 5 cc. 2/m NaCl+80 cc. H_2O.
5. 15 cc. n/10 HCl+10 cc. 2/m NaCl+75 cc. H_2O.
6. 15 cc. n/10 HCl+15 cc. 2/m NaCl+70 cc. H_2O.

The relative degrees of solution of the gelatin after a residence in these mixtures of eighteen hours is indicated in Fig. 154. The addition of the salt has decreased the amount of the gelatin that goes into solution in the hydrochloric acid, and this the more the higher the concentration of the added salt.

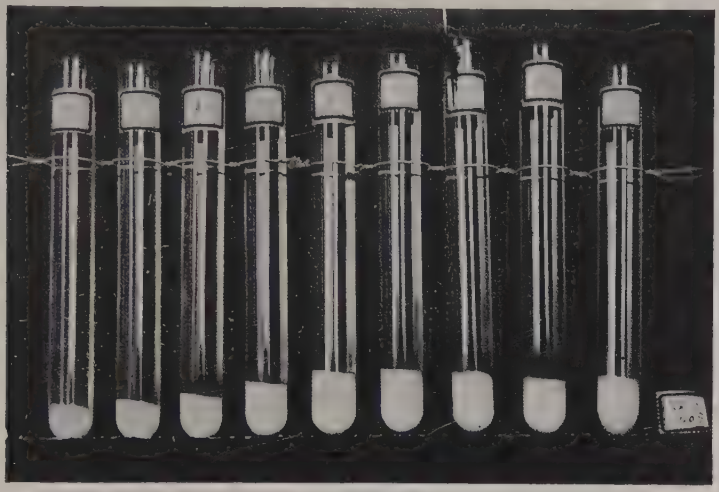


FIGURE 153.

EXPERIMENT 74.—Five leaves of dry gelatin weighing altogether 0.4 gram and having the same surface were placed in each of the following solutions:

1. 15 cc. n/10 HCl+85 cc. H_2O.
2. 15 cc. n/10 HCl+10 cc. m/1 sodium acetate+75 cc. H_2O.
3. 15 cc. n/10 HCl+10 cc. m/1 sodium chlorid +75 cc. H_2O.
4. 15 cc. n/10 HCl+10 cc. m/1 sodium nitrate +75 cc. H_2O.
5. 15 cc. n/10 HCl+40 cc. m/4 disodium hydrogen phosphate +45 cc. H_2O.
6. 15 cc. n/10 HCl+40 cc. m/4 sodium sulphate+45 cc. H_2O.
7. 15 cc. n/10 HCl+10 cc. m/1 sodium citrate +75 cc. H_2O.

The relative amounts of gelatin dissolved in these various solutions after the gelatin leaves had with occasional agitation remained in them for $19\frac{1}{2}$ hours are indicated in Fig. 155. As is readily evident, each of the salts decreases by its presence the amount of gelatin dissolved in the acid solution. The bivalent and trivalent acid radicals are more powerful in this respect than the monovalent ones, with the exception of the acetate. The intermediate position taken by this radical, in this matter of the solution of the gelatin, corresponds with the intermediate position occupied by this same radical in the swelling of the colloid under similar circumstances.

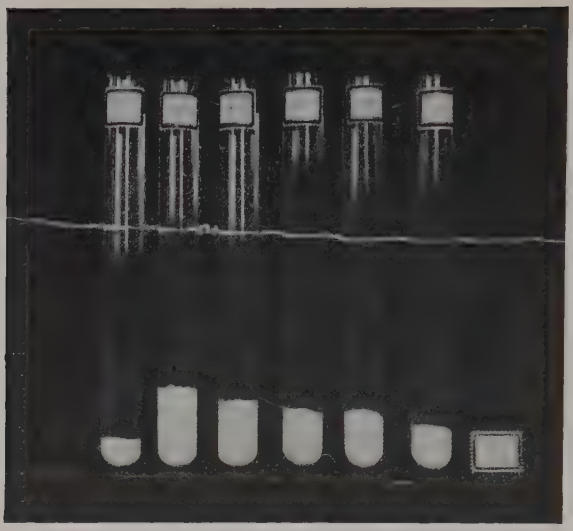


FIGURE 154.

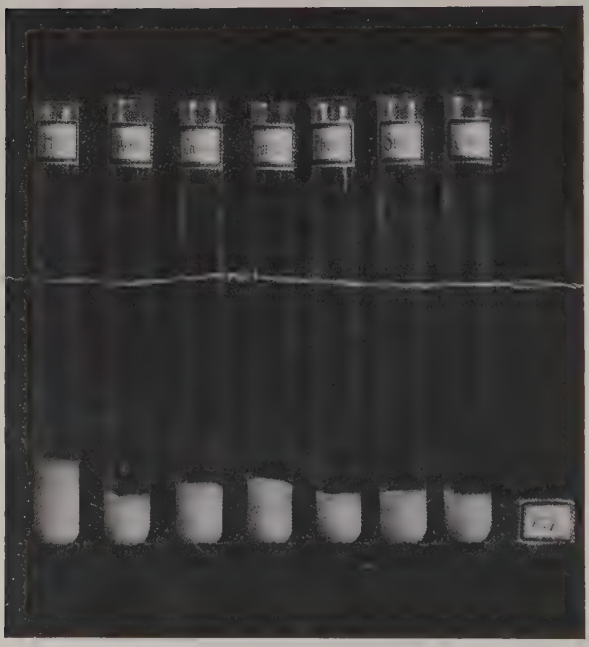


FIGURE 155.

These experiments show that the "solution" of two typical protein colloids is intimately connected with the character of the medium surrounding them. Acids (and alkalies) favor their solution, while various other substances (notably salts) either do not affect it at all, or when present in conjunction with an acid (or alkali) depress the amount that would have been "dissolved" if the acid (or alkali) had been present alone.

Let us now recall that what lies between the urine on the one hand and the blood on the other (the kidney) is made up physico-chemically of just such colloid gels as these under discussion. Furthermore, we learned above that under normal circumstances, in "health," in other words, conditions are such in the kidney that this gel state is maintained. But in nephritis the acid content of the kidney is increased, in consequence of which conditions are offered which permit these protein colloids to pass over into the sol state and so escape with the urine. *Albuminuria results whenever some or all of the colloid gels that constitute the urinary membrane go into "solution" in the urine, and this is made possible under the same conditions which permit fibrin or gelatin gels to "dissolve" in water.* We shall find further evidence in support of this belief as we proceed.

If it is true that albuminuria represents merely a "solution" of the kidney proteins in the urine, if, in other words, it does not come from the blood (except in that indirect way in which the proteins of any cell come originally from the blood), then albuminuria cannot be that strange and specific thing which as clinicians we are likely to think it. *Any cell must, under conditions similar to those existing in the kidney when this is nephritic, be capable of serving as a source of albumin to a surrounding liquid medium, and so be capable of being responsible for a state which in the kidney goes by the name of "albuminuria."* A little thought will show that such actually is the case.

Every worker in the biological sciences is familiar with the ancient fact that "dead" organisms allow the escape of protein from them. A frog or fish living in its aquarium does not impart a protein reaction to the water. But let it die and in a few hours the previously clear water gives a positive result when tested for albumin, and this reaction becomes the more intense as time goes on. What happens is that after death the tissues

develop the familiar postmortem acids and under their influence some of the proteins now go into "solution" in the surrounding medium. Such "solution" occurs whether the organism is a simple or complex one. Only when a simple organism possessing no circulatory system thus serves as a source of albumin then we can no longer talk about a "filtering" off of albumin, an "increased permeability of vessel walls," etc.,—as we should not in the discussion of the albuminuria of nephritis.

But we need not wander so far away from the mammals, or in fact the living animal itself, in order to show that "albuminuria" is not the specific thing we think it. As surgeons well know, the normal intestinal juices scarcely yield an albumin test, yet the fluid contained in a strangulated hernia or a volvulus is rich in albumin. Here the interference with the circulation to the gut, produced through the strangulation or the twist, has placed a section of the bowel in a state of lack of oxygen; it develops in consequence an abnormally high acid content, and so some of the proteins of the gut wall go into "solution"—in other words, we get in the bowel what in the kidney is called albuminuria.

Analogous conditions come to pass in the parenchymatous organs. When these are placed under circumstances which lead to an increase in their acid content, a state analogous to the albuminuria of the kidney results. The lymph coming from a muscle that is made to work hard has a higher albumin content than that coming from this same muscle when at rest, and when the circulation through the liver is impeded (I would say oxygen supply through the hepatic artery is interfered with), either through ligation of the inferior vena cava or obturation of the thoracic aorta, the albumin content of the lymph coming from this organ begins to rise, as E. H. Starling[1] has clearly shown. In glaucoma the albumin content of the fluid of the anterior chamber rises, and in œdema of the brain and cord the cerebro-spinal fluid shows a more than usual amount of protein.[2]

[1] E. H. Starling: Jour. Physiol., **16**, 224 (1894); **17**, 30 (1895); see also Bayliss and Starling: ibid., **16**, 159 (1894).

[2] Edmund M. Baehr: Personal communication (1913).

3. On the Relation between Swelling and Solution in Protein Colloids [1]

The importance of the swelling and of the liquefaction or "solution" [2] of protein colloids for the interpretation of such biological problems as œdema and albuminuria and the fact that the same external changes influence both and in the same general direction compels inquiry regarding the relation between the two.

It is a commonly accepted view that the "solution" of a protein represents but the extreme of that which in lesser degree is called swelling. So far as I know, it has been held almost universally that sufficient hydration results as a matter of course in "solution." Careful investigation of the problem, however, shows that this is *not* the case. The matter is easily proved by working with such a protein as gelatin at concentrations and temperatures near its gelation or melting point. Since acids and alkalies increase hydration, the addition of these substances to a barely liquid gelatin-water mixture ought to stiffen it. As a matter of fact just the reverse occurs. By working instead with a stiff gelatin, a previously solid mixture is made to liquefy upon the addition of these substances. *The phenomena of swelling (hydration) and of "solution" in protein gels while frequently associated are therefore essentially different. Swelling is best understood as a change whereby the protein enters into physico-chemical combination with more of the solvent (water), as a change in the direction of greater solubility of the solvent in the protein; "solution" is best conceived of as a change in the direction of greater solubility (an increased degree of dispersion) of the colloid in the solvent.* If reference is made to Fig. 3 (page 56) it will be noted that changes involving swelling occur in the region below the level marked *V*; changes in the direction of liquefaction or "solution" above the level marked *E*.

§ 1

The experiments which seem to justify these deductions were carried out as follows. A high grade commercial gelatin low in

[1] Martin H. Fischer: Science, **42**, 223 (1915); Kolloid-Zeitschr., **17**, 1 (1915).

[2] Since there are many minds regarding the nature of solution, accurate definition of the term is not easy. I am here using the term in its broadest sense as covering everything, in the case of the colloids, from their liquefaction point upwards to the accepted "true" solution of the physical chemists.

salts was used and one which previous experiments had shown to be capable of setting into a firm jelly at very low concentrations. From this there was prepared a homogeneous 10 per cent stock solution which was then used in the various series of experiments. After having once obtained this stock, all unnecessary further heating of the gelatin was avoided. To prepare the various gelatin mixtures the stock gelatin was warmed to slightly above its liquefaction point and, after mixing with the necessary reagents in test tubes of uniform diameter, the mixtures were all reduced to the temperature of 25° C. as rapidly as possible and kept there. Precautions were taken to treat every set of tubes in each of the series of experiments exactly alike so far as methods of mixing, exposure to changes in temperature, etc., were concerned.

An 0.8 to 0.9 per cent solution of the stock gelatin would set into a solid mass, permitting the test tube to be turned over without having the contents flow, when left to itself for a few hours at 25° C. It having been determined in this fashion that any gelatin-water mixture above a 1 per cent concentration of this gelatin would remain solid, the following Experiment 75 with a 2 per cent gelatin was carried out in order to discover whether the addition of acid to the gelatin would increase or decrease its tendency to gel. Since acids increase the power of protein colloids to swell (and increase the viscosity of gelatin sols) it was to be expected, on a priori grounds, that the addition of acid would tend to increase the tendency of gelatin to gel. *As the following shows, the addition of acid very markedly decreases the tendency of gelatin to gel* (*increases its tendency to "dissolve"*).

Experiment 75.—

1. 2 cc. 10% gelatin+8 cc. H_2O.
2. 2 cc. 10% gelatin+0.1 cc. n/10 HCl+7.9 cc. H_2O.
3. 2 cc. 10% gelatin+0.2 cc. n/10 HCl+7.8 cc. H_2O.
4. 2 cc. 10% gelatin+0.3 cc. n/10 HCl+7.7 cc. H_2O.
5. 2 cc. 10% gelatin+0.4 cc. n/10 HCl+7.6 cc. H_2O.
6. 2 cc. 10% gelatin+0.5 cc. n/10 HCl+7.5 cc. H_2O.
7. 2 cc. 10% gelatin+1.0 cc. n/10 HCl+7.0 cc. H_2O.
8. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+6.5 cc. H_2O.
9. 2 cc. 10% gelatin+2.0 cc. n/10 HCl+6.0 cc. H_2O.
10. 2 cc. 10% gelatin+2.5 cc. n/10 HCl+5.5 cc. H_2O.
11. 2 cc. 10% gelatin+3.0 cc. n/10 HCl+5.0 cc. H_2O.

After these mixtures had stood for twenty-four hours the control gelatin mixture in tube 1 was perfectly solid. The mixtures in tubes 2, 3, 4,

5 and 6 were so solid that they could be turned over, though on hard shaking the surfaces in the two last named could be made to quiver. In tube 7 the gelatin flowed as a viscid liquid. In tubes 8, 9, 10 and 11 the mixtures were entirely fluid.

Just as the presence of acid liquefies gelatin so does that of alkali. This is shown in Experiment 76.

Experiment 76.

1. 2 cc. 10% gelatin+8 cc. H_2O.
2. 2 cc. 10% gelatin+0.1 cc. n/10 NaOH+7.9 cc. H_2O.
3. 2 cc. 10% gelatin+0.2 cc. n/10 NaOH+7.8 cc. H_2O.
4. 2 cc. 10% gelatin+0.3 cc. n/10 NaOH+7.7 cc. H_2O.
5. 2 cc. 10% gelatin+0.4 cc. n/10 NaOH+7.6 cc. H_2O.
6. 2 cc. 10% gelatin+0.5 cc. n/10 NaOH+7.5 cc. H_2O.
7. 2 cc. 10% gelatin+1.0 cc. n/10 NaOH+7.0 cc. H_2O.
8. 2 cc. 10% gelatin+1.5 cc. n/10 NaOH+6.5 cc. H_2O.
9. 2 cc. 10% gelatin+2.0 cc. n/10 NaOH+6.0 cc. H_2O.
10. 2 cc. 10% gelatin+2.5 cc. n/10 NaOH+5.5 cc. H_2O.
11. 2 cc. 10% gelatin+3.0 cc. n/10 NaOH+5.0 cc. H_2O.

After standing for twenty-four hours at 25° C. the gelatin in tube 1 was solid; that in tubes 2, 3, 4 and 5 was also solid; in tube 6 the surface quivered on shaking. The gelatin in tube 7 flowed as a viscid liquid. In the remaining tubes the gelatin was entirely liquid.

To show that the presence of acid or alkali will not only prevent the gelation of gelatin, but that it will liquefy this after gelation has occurred, Experiment 77 is introduced.

Experiment 77.—

1. 2 cc. 10% gelatin+8 cc. H_2O.
2. 2 cc. 10% gelatin+0.3 cc. n/10 HCl+7.7 cc. H_2O.
3. 2 cc. 10% gelatin+0.5 cc. n/10 HCl+7.5 cc. H_2O.
4. 2 cc. 10% gelatin+1.0 cc. n/10 HCl+7.0 cc. H_2O.
5. 2 cc. 10% gelatin+2.0 cc. n/10 HCl+6.0 cc. H_2O.
6. 2 cc. 10% gelatin+3.0 cc. n/10 HCl+5.0 cc. H_2O.
7. 2 cc. 10% gelatin+8 cc. H_2O.
8. 2 cc. 10% gelatin+0.3 cc. n/10 NaOH+7.7 cc. H_2O.
9. 2 cc. 10% gelatin+0.5 cc. n/10 NaOH+7.5 cc. H_2O.
10. 2 cc. 10% gelatin+1.0 cc. n/10 NaOH+7.0 cc. H_2O.
11. 2 cc. 10% gelatin+2.0 cc. n/10 NaOH+6.0 cc. H_2O.
12. 2 cc. 10% gelatin+3.0 cc. n/10 NaOH+5.0 cc. H_2O.

In this series the gelatin and water were first mixed and, at the end of twenty-four hours when the gelatin mixtures had solidified, the acid or alkali was dropped upon them. At the end of the second twenty-four hours the following was observed. Control tubes 1 and 7 containing only

pure gelatin were solid. Decrease in viscosity to complete liquefaction of the gelatin was observable in the remaining tubes. As more than twenty-four hours is required for the acid to diffuse through the entire depth of the gelatin, the upper portions of the gelatin columns showed the greatest amount of change. In tubes 2 and 3 and tubes 8 and 9 there was a distinct softening of the upper portions of the gelatin column. The upper half of tubes 4 and 10 flowed as a viscid liquid. In tubes 5 and 6 and tubes 11 and 12 the gelatin was liquefied almost to the bottom of the tubes.

Since different salts decrease the tendency of various proteins to swell in the presence of an acid or an alkali it was to be expected that their addition to an acid or alkali-gelatin mixture should liquefy further such a mixture provided swelling and solution were identical processes. Experiment 78 shows again that just the opposite occurs. *The addition of sodium chlorid tends to counteract the liquefying effect of an acid.*

Experiment 78.

1. 2 cc. 10% gelatin+8 cc. H_2O.
2. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+6.5 cc. H_2O.
3. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+0.1 cc. m/1 NaCl +6.4 cc. H_2O.
4. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+0.2 cc. m/1 NaCl +6.3 cc. H_2O.
5. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+0.3 cc. m/1 NaCl +6.2 cc. H_2O.
6. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+0.4 cc. m/1 NaCl +6.1 cc. H_2O.
7. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+0.5 cc. m/1 NaCl +6.0 cc. H_2O.
8. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+1.0 cc. m/1 NaCl +5.5 cc. H_2O.
9. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+2.0 cc. m/1 NaCl +4.5 cc. H_2O.
10. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+3.0 cc. m/1 NaCl +3.5 cc. H_2O.
11. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+4.0 cc. m/1 NaCl +2.5 cc. H_2O.
12. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+5.0 cc. m/1 NaCl +1.5 cc. H_2O.

Twenty-four hours after the mixtures had been prepared the pure gelatin in tube 1 was solid; the acidified gelatin in tube 2 was liquid. A distinct influence of the sodium chlorid in inhibiting the solvent action of the acid was evident even in tube 3 where the mixture barely flowed. The viscosity increased progressively from tubes 4 to 7 in which the optimum effect of the sodium chlorid in restraining liquefaction was observed.

Here the gelatin was solid, but not quite so solid as the pure gelatin. The gelatin mixtures in tubes 8, 9 10, 11 and 12 were solid, but on tapping quivered more easily than did the gelatin in tube 7.

Experiment 79, similar in arrangement to Experiment 78, brings out the same facts for an alkali-gelatin series. Sodium chlorid inhibits the liquefying action of sodium hydroxid as it did that of acid.

Experiment 79.

1. 2 cc. 10% gelatin+8 cc. H_2O.
2. 2 cc. 10% gelatin+1.5 cc. n/10 NaOH+6.5 cc. H_2O.
3. 2 cc. 10% gelatin+1.5 cc. n/10 NaOH+0.1 cc. m/1 NaCl +6.4 cc. H_2O.
4. 2 cc. 10% gelatin+1.5 cc. n/10 NaOH+0.2 cc. m/1 NaCl +6.3 cc. H_2O.
5. 2 cc. 10% gelatin+1.5 cc. n/10 NaOH+0.3 cc. m/1 NaCl +6.2 cc. H_2O.
6. 2 cc. 10% gelatin+1.5 cc. n/10 NaOH+0.4 cc. m/1 NaCl +6.1 cc. H_2O.
7. 2 cc. 10% gelatin+1.5 cc. n/10 NaOH+0.5 cc. m/1 NaCl +6.0 cc. H_2O.
8. 2 cc. 10% gelatin+1.5 cc. n/10 NaOH+1.0 cc. m/1 NaCl +5.5 cc. H_2O.
9. 2 cc. 10% gelatin+1.5 cc. n/10 NaOH+2.0 cc. m/1 NaCl +4.5 cc. H_2O.
10. 2 cc. 10% gelatin+1.5 cc. n/10 NaOH+3.0 cc. m/1 NaCl +3.5 cc. H_2O.
11. 2 cc. 10% gelatin+1.5 cc. n/10 NaOH+4.0 cc. m/1 NaCl +2.5 cc. H_2O.
12. 2 cc. 10% gelatin+1.5 cc. n/10 NaOH+5.0 cc. m/1 NaCl +1.5 cc. H_2O.

At the end of twenty-four hours the pure gelatin was solid; the gelatin plus the alkali was liquid. The tubes containing sodium chlorid in addition were all solid, the optimum effect of the salt again being evident in tube 7.

Sodium chlorid antagonizes the liquefying action of acid only when the latter is not present in too high concentration. In other words, with a given concentration of sodium chlorid an increase in the acid content will again serve to liquefy the gelatin. This is shown in Experiment 80, in which different amounts of acid are added to a gelatin-salt mixture of constant concentration.

EXPERIMENT 80.

1. 2 cc. 10% gelatin+8 cc. H_2O.
2. 2 cc. 10% gelatin+1 cc. m/1 NaCl+7 cc. H_2O.
3. 2 cc. 10% gelatin+1 cc. m/1 NaCl+1.0 cc. n/10 HCl +6 cc. H_2O.
4. 2 cc. 10% gelatin+1 cc. m/1 NaCl+1.5 cc. n/10 HCl +5.5 cc. H_2O.
5. 2 cc. 10% gelatin+1 cc. m/1 NaCl+2.0 cc. n/10 HCl +5.0 cc. H_2O.
6. 2 cc. 10% gelatin+1 cc. m/1 NaCl+2.5 cc. n/10 HCl +4.5 cc. H_2O.
7. 2 cc. 10% gelatin+1 cc. m/1 NaCl+3.0 cc. n/10 HCl +4.0 cc. H_2O.
8. 2 cc. 10% gelatin+1 cc. m/1 NaCl+3.5 cc. n/10 HCl +3.5 cc. H_2O.
9. 2 cc. 10% gelatin+1 cc. m/1 NaCl+4.0 cc. n/10 HCl +3.0 cc. H_2O.
10. 2 cc. 10% gelatin+1 cc. m/1 NaCl+4.5 cc. n/10 HCl +2.5 cc. H_2O.
11. 2 cc. 10% gelatin+1 cc. m/1 NaCl+5.0 cc. n/10 HCl +2.0 cc. H_2O.

At the end of twenty-four hours the pure gelatin in tube 1 was solid as was also the pure sodium chlorid-gelatin mixture in tube 2. Tube 3 contained an amount of acid which, as shown in Experiment 75, was able to keep gelatin from solidifying. In the presence of sodium chlorid, however, this gelatin mixture was found to be solid. The liquefying action of the acid concentrations in tubes 4 and 5 was also so restrained by the chlorid that in these the gelatin merely quivered on tapping. In tubes 6 and 7 the gelatin almost flowed, and in tubes 8, 9, 10 and 11 it did this in progressing degree.

Experiment 81 shows the effect of a salt with a bivalent acid radical, Experiment 82 of one with a bivalent basic radical.

EXPERIMENT 81.

1. 2 cc. 10% gelatin+8 cc. H_2O.
2. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+6.5 cc. H_2O.
3. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+0.4 cc. m/1 Na_2SO_4 +6.1 cc. H_2O.
4. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+0.8 cc. m/1 Na_2SO_4 +5.7 cc. H_2O.
5. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+1.2 cc. m/1 Na_2SO_4 +5.3 cc. H_2O.
6. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+2.0 cc. m/1 Na_2SO_4 +4.5 cc. H_2O.
7. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+4.0 cc. m/1 Na_2SO_4 +2.5 cc. H_2O.

Twenty-four hours later the gelatin in tube 1 was solid; in tubes 2 and 3 liquid; in tube 4 the contents were viscid; tube 5 could be turned over; the gelatin tubes 6 and 7 were solid.

EXPERIMENT 82.

1. 2 cc. 10% gelatin+8 cc. H_2O.
2. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+6.5 cc. H_2O.
3. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+0.1 cc. m/1 $CaCl_2$+6.4 cc. H_2O.
4. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+0.2 cc. m/1 $CaCl_2$+6.3 cc. H_2O.
5. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+0.3 cc. m/1 $CaCl_2$+6.2 cc. H_2O.
6. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+0.5 cc. m/1 $CaCl_2$+6.0 cc. H_2O.
7. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+1.0 cc. m/1 $CaCl_2$+5.5 cc. H_2O.
8. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+1.5 cc. m/1 $CaCl_2$+5.0 cc. H_2O.
9. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+2.0 cc. m/1 $CaCl_2$+4.5 cc. H_2O.
10. 2 cc. 10% gelatin+1.5 cc. n/10 HCl+2.5 cc. m/1 $CaCl_2$+4.0 cc. H_2O.

After twenty-four hours the pure gelatin in tube 1 was solid; that containing acid in tube 2 liquid; the mixtures in tubes 3 and 4 were viscid; in tube 5, almost solid; in tube 7, entirely solid. Beyond this concentration the stiffness of the gelatin mixtures again decreased until that in tube 10 was again liquid.

In order not to drag out these detailed observations to unnecessary lengths it may be said that, in general, all salts act upon an acidified or alkalinized gelatin. There exist, however, certain quantitative and qualitative differences when different salts are employed. When salts with a common base but different acid radicals are compared, it is found that chlorids, bromids, nitrates, iodids and sulphocyanates produce about equal effects; acetates and sulphates hold a middle position while citrates and tartrates are most powerful. On the other hand, with a common acid radical the monovalent salts are less powerful than the bivalent, and these than the trivalent. How these findings may be understood is indicated in the next paragraph.

§ 2

The above experiments show that the swelling of a hydrophilic colloid like gelatin and its liquefaction or solution while frequently

associated processes are in essence distinct in character. An attempt made earlier[1] to explain what happens in these proteins we think no longer adequate. The answer to what seems really to happen appears in some later studies on the colloid chemistry of soaps.[2]

We now hold to the view that protein, regarded in its simplest form as a polymerized amino-acid, behaves colloid-chemically like the ordinary fatty acids which in combination with different bases form the various soaps. Each of these soaps or soap-like compounds has its own capacity for taking up water (swelling) and solubility in water. Speaking generally, the soaps of the alkali metals have the greatest capacity for taking up water and the greatest solubility in water. The soaps of the alkaline earths occupy a middle position while the soaps of the heavier metals take up but little water and are scarcely soluble in water. *The same is true for the metal proteinates.*

While the fatty acids are capable of combining only with bases the amino (fatty) acids, as found in protein, may thus combine not only with bases but with acid. This gives a second series of protein salts which, dependent upon the kind of acid introduced in the protein, yield protein hydrochlorid, protein sulphate, etc. *Each of these protein compounds has again its characteristic solvent powers for water and solubility in water.*

If the above facts are kept in mind, all of the hydration and solubility characteristics of gelatin or any other protein are easily understood. As we vary in a protein-water system the concentration or kind of acid, alkali or salt we form different basic and acidic derivatives of the original protein (amino-acid) and the swelling and solubility characteristics of the system are an expression of the character of these fundamental compounds.

This first and fundamental chemical arrangement within the mixture of the protein salt molecules is, however, not sufficient to explain all the changes observed in such systems as have been described. The characteristic features of what happens whenever gelatin, acid and salt or gelatin, alkali and salt are mixed together is well shown in Experiments 78 and 79. With increas-

[1] Martin H. Fischer: Kolloid-Zeitschr., **27**, 5 (1915).

[2] Marian O. Hooker and Martin H. Fischer: Chem. Engineer, **27**, 159, 223, 253 (1919); Martin H. Fischer: Chem. Engineer, **27**, 184, 271 (1915). A running account appears in Soaps and Proteins, New York (1920), *in press.*

ing concentration of the added salt to an acid or alkali gelatin there is observed, first, an increase in viscosity, resulting later in solidification, followed by a secondary fall in viscosity or liquefaction which, when enough salt is added, ends in a separation of the protein in practically anhydrous fashion from the mixture. These changes follow even when the salt is so chosen as to preclude the possibilities of chemical reaction with the protein compound. To understand what happens under such circumstances it is well to emphasize the parallelism existing between these changes in proteins and those observed in the salting-out of soap.[1]

If we attempt to explain the successive changes which follow the addition of a salt to the acid or alkali protein and try to do this without recourse to too many violent assumptions the following seems the simplest way out.

The entire series of changes observed in the salting-out of an acid or alkali protein by a salt is readily understood if it is assumed that the added neutral salt unites with the solvent to form a hydrate or solvate and that the consequent viscosity changes (including gelation) are those dependent upon the changes in viscosity observed whenever any one liquid is emulsified in a second. It does not matter for our purposes whether such union with the "solvent" is brought about by the molecules or the ions or any other derivatives of the salt. *The solvates (hydrates) after being formed then separate out in dispersed form in the acid or alkali protein.*

Diagrammatically the successive changes are illustrated in Fig. 156. If, to simplify matters, we represent the original pure acid or alkali protein " solution " as a homogeneous system [2] as indicated in tube *A* of Fig. 156, the effect of adding some molecules of salt may be represented by the diagram marked *B*. Hydration of the salt molecules has two effects, (1) it withdraws water from the original acid or alkali protein system and thus through increase in the concentration of the acid or alkali protein tends to stiffen the system. But this effect is probably not large as compared with (2) *the effects upon viscosity of the dispersion of one material in a second.* The increase in viscosity due to such subdivision of one material in a second is observed under widely varying circum-

[1] Martin H. Fischer: Science, **49**, 616 (1919); Chem. Engineer, **27**, 257 (1919).

[2] It is at least a di-phasic system, as emphasized in Chem. Engineer, **27**, 184 (1919), but for our purposes we will call it a mono-phasic one.

THEORY OF GELATION

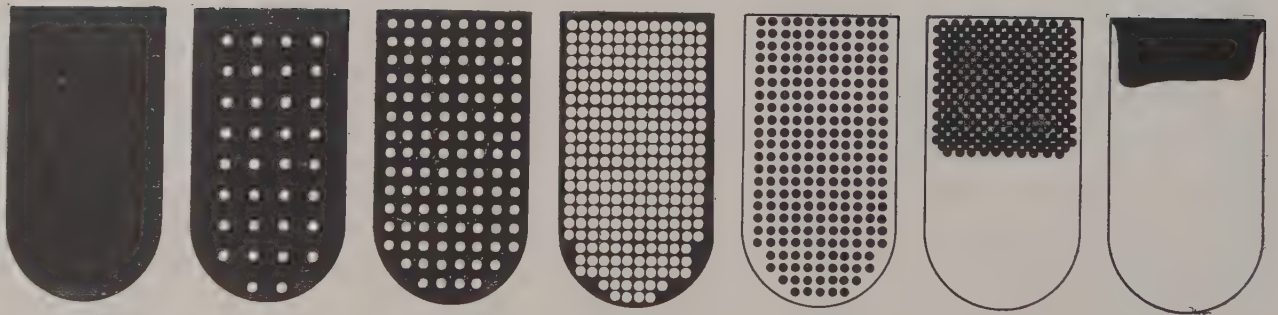


FIGURE 156.

stances. A good example for our purposes is that represented by the increase in viscosity when one liquid (like cottonseed oil) is emulsified in a second (like a soap solution). The "mayonnaise" which results may become so stiff that it will stand alone.

The viscosity of such di-phasic systems—and it is well for our purposes to bear in mind particularly di-phasic systems consisting of one liquid dispersed in a second or of a solid dispersed in a liquid—increases with every increase in the concentration of the internal dispersed phase and with every decrease in the size of the individual dispersed particles. The viscosity of an emulsion of liquid oil in liquid soap, for instance, increases as more and more oil is beaten into the soap; or, on the other hand, with a given amount of oil subdivided into a given volume of soap the viscosity of the mixture is increased if a previously coarse emulsion is made more fine by "homogenizing."

It is such increase in the number of hydrated salt particles with increasing concentration of the added salt that explains the progressive increase in the viscosity (see diagram *C*) which, when the amount of water in the system is not too high, culminates in gelation. If the concentration of the salt is still further increased, the time approaches when the number (or size) of the hydrated salt particles becomes so great that they touch each other (diagram *D*). When this happens a critical point has been reached and there must appear a change in the type of the system, *for the hydrated salt particles now become the continuous external phase while the acid or alkali protein particles form the internal divided phase.* Such change in type of emulsion even without change in the quantitative relationships of the two liquids composing the emulsion is regularly followed by a change in viscosity. This situation is indicated in tube *E* of Fig. 156. The viscosity of the system now tends in the direction of the salt solution and so, with further additions of salt, falls. *This is the region of secondary liquefaction after the region of gelation in our experiments.* At this point, however, the acid or alkali protein system also shows the first evidences of becoming turbid. This is because more and more water has been taken from the protein and as this becomes dehydrated its index of refraction changes. Being different from that of the dispersion medium the mixture appears milky. The dehydrated acid or alkali protein particles being possessed of a lower specific gravity than that of the salt solution

constituting the dispersion medium begin to float to the top as indicated over *F* in Fig. 156. When enough salt has been added to the system, the protein is entirely dehydrated, as shown in diagram *G*.

4. Critical Remarks

It has been argued by some of my critics that the "solution" theory of albuminuria fails because the amounts of albumin given off by a kidney may be so large that were it all due to solution the whole kidney would be lost in a short time. Before this plausible objection is accepted it is well to consider the following rather obvious facts. In the first place, the albuminuria which we are discussing and the mechanism of which is a matter of debate is only that which is observed *even though the blood vessels are intact.* No one questions the vascular origin of the protein derived from frankly ruptured and oozing blood vessels or from red and white blood corpuscles which have escaped through the substance of the kidney into the urine and died there (diapedesis with subsequent " solution " of the escaped cells).

We are likely to find the largest amounts of albumin without gross blood vessel lesions in the earlier stages of the acute types of nephritis, say in the pregnancy or other toxic nephritides. Suppose we choose a figure high enough to suit everybody and say that 20 grams of albumin are being given off to the liter of urine. Such kidneys are not likely to be secreting more than 100 or 200 cc., but suppose they are putting out 500. Even so, only 10 grams of albumin are being lost daily and we have 300 or more grams of kidney tissue to work on. But such albuminurias are neither common nor do they last long—the patient either gets over them in a very few days or dies.

In the chronic types of nephritis we encounter no such figures. But even those that are observed cannot without revision be credited to that essential albuminuria which alone needs discussion. Thus, in chronic interstitial nephritis associated with vascular disease the blood vessels in the kidney commonly rupture and bleed as they do elsewhere in the body; hemorrhage by diapedesis occurs in all types of kidney disease; and leucocytes not infrequently wander into the kidney tissues and through them into the urine. If the urine has not the right salt concentration, or is a little too acid or alkaline, all these cellular elements

are destroyed and the dissolved protein from this source is added to the exuded blood plasma, and both together are added to that derived from solution of the kidney itself. In this way the latter figure may be pushed to any height, but to say that such an amount of albumin has come from the kidney itself may suit a critic, but it is wrong. Aside from the fact that if a patient lost a gram of protein daily it would take months to destroy enough of his kidney substance to make him aware of it, this presupposes that a kidney has no regenerative powers, which, as a matter of fact, it has equally with other parenchymatous organs. *A testicle, for instance, produces enough sperm daily to total several times its own weight in a year, and yet at the end of that time it has not disappeared.*

We need in this place to consider also an editorial criticism of the Journal of the American Medical Association.[1] Its heading "A Controverted Theory of Nephritis" has been chosen a little broadly, for the paragraph itself comments only on the work of G. Salus,[2] who in connection with his serological studies touches on the solution theory of albuminuria. Salus found that he could develop a precipitin for human blood serum by using albuminous urine as an antigen. He concludes correctly from this, that the albumin in his urines contained blood proteins. But then no one has ever disputed this fact, for hemorrhage through gross rupture of the blood vessels and by diapedesis is common in all types of nephritis.

On the other hand, he found that he could get no response (more accurately stated, but one in ten trials) when he added the antiserum prepared from albuminous urine to a solution of tissue proteins extracted from the kidney. He cites this as evidence against the presence of dissolved kidney protein in the urine. In the face of the fact that it is difficult to prepare a specific antiserum even when kidney substance is used directly, such findings are hardly conclusive. The colloid chemists, moreover, know how alterable in consequence of mere laboratory handling are the reactions of proteins, and so some argument will be necessary to make those of solid organs and of organ extracts synonymous in their minds. Salus himself recognizes these difficulties but the editorial writer seems unaware of them.

[1] Editorial: Jour. Am. Med. Assoc., **62**, 1971 (1914).
[2] G. Salus: Biochem. Zeitschr., **60**, 1 (1914).

VI

THE MORPHOLOGICAL CHANGES IN THE KIDNEY

1. Introduction

Anyone who has on the one hand busied himself with the clinical, or as we might better say, the biochemical, aspects of nephritis, on the other with the morphological aspects of this same problem, as this has been developed for us during the last two or three decades, must be struck by the fact that the two have not alone grown up practically independently of each other, but that they have made but slight effort to find common ground.

As a matter of fact, when we attempt to find a connection between the comparatively simple biochemical characteristics of nephritis and the elaborate morphological analyses of the organs from patients who have clinically shown the biochemical marks of a nephritis, this is at first sight not easy. Even if we ignore the fact that much of that which is supposed to characterize nephritis morphologically has nothing to do with the albuminuria, the changes in the secretion of water, the changes in the secretion of dissolved substances, etc., which are the distinguishing marks of a nephritis biochemically, there still remains an apparent lack of connection between the facts, to which any clinician or pathologist will testify, namely, that individuals may die of an acute Bright's disease and show surprisingly little macroscopic or microscopic change in the kidney, while others, never affected with any symptoms referable to the urinary system, may show on autopsy the infant-sized kidneys of chronic interstitial nephritis. And yet if we will but free our minds from the erroneous conclusions to which the temptations of elaborate fixing and staining methods and high power microscopes have led us, it is an easy matter to see that all the morphological changes that occur in a kidney, the seat of an acute or chronic nephritis, are fundamentally simple in character, and that they are easily brought into connection with the clinical manifestations of the disease. We will discover at the same time that the essential morphological changes of acute and chronic nephritis were recognized and a satisfactory classification of the nephritides on morphological

grounds was made decades ago, more especially by WEIGERT,[1] and that a classification of the nephritides on the basis of pathological physiology brings us in these modern days back to yet older teachings, to those of F. T. FRERICHS,[2] for example, who regarded all the nephritides to be in essence the same.

2. Classification of the Nephritides. Correlation of the Morphological Changes in the Kidneys with Some Clinical Manifestations

There is but one kind of nephritis—parenchymatous nephritis. How could there be any other? It is the function of the kidney to yield a secretion which we call urine, and this function is exhibited by the parenchyma of which the kidney is composed. A disturbed kidney function can come to pass only as the parenchyma has been involved. Histological examination shows that the parenchyma is not everywhere the same, and it is presumable therefore that the different parts play different rôles, but since the physiologists have not yet settled what are these differences in the functions of the glomeruli, the convoluted tubules, the collecting tubules, etc., a more detailed classification into glomerular, tubular, etc., types is, to say the least, premature. We know not a single experimental procedure or pathological process which involves exclusively only one of these structures, and we cannot in consequence do more than speculate on their function.

It is evident that a pathological process may involve a whole kidney, in which case we may speak of a *generalized parenchymatous nephritis*, or it may involve only smaller or larger patches, leaving healthy kidney between, in which case we may speak of a *focal* or *spotty parenchymatous nephritis*. Either of these types may, of course, be acute or chronic. If the agencies attacking the kidney are removed, and if the damage done the parenchyma has not been too great, then, evidently, the involved cells may recover, in other words, the normal state of the kidney be re-established. Expressed more technically, recovery occurs if the changes induced in the kidney remain of a *reversible*

[1] The most accessible of WEIGERT'S papers on nephritis appear in Virchow's Archiv during the years 1860 to 1875.

[2] F. T. FRERICHS: Die Bright'sche Nierenkrankheit, Braunschweig (1851).

type. But if for any reason, say through prolonged or particularly intense action of the agencies producing the nephritis, *irreversible* changes occur in the kidney parenchyma, then the involved cells die and are absorbed. If the defect is not or cannot be made good by regeneration of new cells, then that portion of the kidney is gone and in its place may appear nothing more than a little scar tissue. All these possibilities of injury with recovery, or injury with death and loss of the involved part may and do occur in nephritis whether it involves a whole kidney or only a patch in it.

Let us consider first the generalized parenchymatous type of nephritis consequent, say, upon an acute intoxication of some kind. It is possible, first of all, for such a kidney to recover entirely. But if such a fortunate ending is not attained, death of the whole kidney is not the only alternative. Larger or smaller pieces may die and be replaced by connective tissue while the remainder of the kidney recovers. There will ultimately result then a kidney which as far as it goes contains normal parenchyma, but in diminished amount, a so-called *secondarily contracted or sclerosed kidney, a so-called chronic interstitial nephritis secondary to generalized parenchymatous nephritis, the "small red kidney"* of the pathologists. Diagrammatically represented, the process may be illustrated by reference to Fig. 157. The rather uniform effect of a poison of some sort circulating through a kidney is illustrated by the black shading under *a*. If pieces of this kidney die and are absorbed while the remainder recovers we get ultimately the secondarily contracted kidney represented under *b*.

If the parenchymatous nephritis is of the focal or spotty type as represented diagrammatically in Fig. 158, *a*, the changes in the parenchyma may again be either reversible (curable) or irreversible (incurable). If they are irreversible the involved patches will again die and be replaced by connective tissue. The ultimate picture is shown in *b* of Fig. 157 and again approximates that previously described. Healthy kidney substance remains to make up the bulk of the kidney which, however, is diminished in amount and has connective tissue scattered through it. We have again a "small red kidney," in other words, again a chronic interstitial nephritis. But because some have assumed—falsely as we shall see—that the connective tissue was laid down first

and that the death and disappearance of parts of the kidney occurred later, this pathological entity has been called a *primarily contracted kidney* or a *primary chronic interstital nephritis.* From a morphological classification point of view this kidney is about the same as the secondarily contracted kidney previously discussed.

It will make matters a little clearer if we try at once to connect up this simple classification with the clinical aspects characteristic of the described kidney states.

If a poison capable of inducing nephritic changes circulates in the body of a patient, let us say the toxins of a scarlet fever, the toxins of a pregnancy nephritis, or bichlorid of mercury, it will, in passing through the kidney, tend on the whole

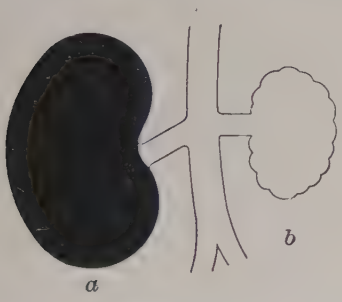


FIGURE 157.

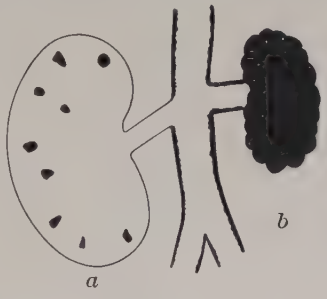


FIGURE 158.

to affect the entire kidney at once and more or less uniformly. For this reason examination in the course of a surgical operation or postmortem reveals the swollen kidney of the so-called generalized parenchymatous nephritis. Since the whole kidney is involved, we encounter under these circumstances the greatest interference with function and therefore the greatest decrease in water output—maybe to the point of complete suppression. At the same time such urine as is secreted is heavily charged with albumin and casts. If the causes operating to produce the nephritis pass away, the kidney recovers and so the urinary output rises again and casts and albumin diminish, all, maybe, in the space of a few days. But if pieces of the kidney die, the evidences of destruction in the kidney as betrayed by casts and albumin may last longer, but even here if the causes operating to produce the nephritis are ultimately overcome, such portions

of the kidney as are left may recover and the patient with his secondarily contracted kidneys—his morphologically chronic interstitial nephritis—may live indefinitely. The reason for this resides in the fact that *one-quarter of our total kidney substance is easily sufficient to maintain us in health* and happiness, and if this amount has been saved the patient need show no signs or symptoms which will allow a diagnosis of his true condition. An autopsy or examination of the kidneys in the course of a surgical operation may offer the first occasion for recognizing the kidney state.

It is hardly possible for a soluble poison to enter the kidney and not affect it rather uniformly. A circulating poison can hardly, therefore, give rise to a spotty or focal parenchymatous nephritis. For such we need a spotty cause. Such is offered, for example, by a seeding of micro-organisms into the kidney (infectious embolism) or by the changes consequent upon vascular disease.[1] We shall return to this problem later, but it may be emphasized here that all evidence shows the vascular disease to be primary and the kidney disease secondary to it.[2] Vascular disease attacks particularly the smallest blood vessels. (When it attacks the larger blood vessels it does this by attacking their vasavasorum.) Since the blood vessels of the kidney do not escape, this organ may, of course, be affected. In consequence of the thickening of the vascular walls and the oft-accompanying thrombotic changes, one piece of the kidney after another is deprived of its blood supply. As this happens they show the changes characteristic of nephritis, and since the arteries involved are end arteries, the kidney changes are largely irreversible, and piece after piece of the kidney dies and disappears while connective tissue takes its place. *The portions of kidney involved in this*

[1] Under this caption I include all the pathological processes capable of affecting the blood vessels, no matter what their assumed causes, be they frank infections as in syphilis, or "degenerations" as in atheroma, arteriosclerosis, etc., popularly regarded as consequent upon attack from that old guard, alcohol, hard work, gout, auto-intoxication, and a meat diet. For further remarks on vascular disease, see pages 615, 629 and 634.

[2] See in this connection, Hauch's beautiful x-ray pictures of the blood vessels of healthy and diseased kidneys. In vascular disease involving this organ the lumina of the blood vessels become smaller and the vessels supplying a given area progressively less in number. When such changes are sufficiently advanced the involved kidney tissues die. Hauch: Fortschr. Röntgenstrahl. **20**, 172 (1913).

localized destruction of kidney parenchyma show all the signs characteristic of parenchymatous nephritis. Between these localized areas of parenchymatous nephritis the kidney tissue is healthy. When, now, we again remember that less than one-fourth of the total kidney substance is necessary for the maintenance of life, it is easy to see why a patient with chronic interstitial nephritis runs along in a fairly normal way. The destruction of the kidney occurs so very slowly that little albumin appears in the urine, and casts only in small numbers. So this patient may also die without ever having become conscious of his kidney state. If a diagnosis is made for him it is done very largely on the basis of findings referable to his vascular disease (palpable blood vessels, high blood pressure, cardiac hypertrophy) which as we shall see are not secondary to his kidney disease, but expressive of his vascular condition.

We shall have occasion to return to all this later. For the present it is sufficient merely to emphasize the fact that the *chronic interstitial nephritis associated with vascular disease is in essence also a parenchymatous nephritis—a slow-going but progressive localized parenchymatous nephritis resulting in death and loss of the involved portions of the kidney and ultimately in a picture which is best described by calling it an atrophy of the kidney.* The patient with chronic interstitial nephritis is, therefore, in the same position as an animal that has had its kidney substance progressively diminished in amount by successive operations and ablations of kidney parenchyma. The man who has gone through life without marked signs or symptoms of kidney disease, who dies of other causes than kidney disease, and shows on the autopsy table what, as *morphologists*, we call chronic interstitial nephritis, is simply like the animal that has suffered a great reduction in total kidney substance, but has not yet reached the physiological minimum compatible with life for that animal under the conditions under which it has to live. What is left of kidney parenchyma to man or animal is still physiologically active and physiologically adequate. Such a biological contention finds its morphological support in the fact that the parenchyma of such (morphologically) chronic interstitial types of nephritis shows little or no change either macroscopically or microscopically (" small red kidney "). The presence of the connective tissue in the kidney is an accident; it is scar tissue, and whatever im-

portance we may care to attach to it morphologically, this is no more expressive of the physiological state of the kidney parenchyma that is left than the scar which repairs and serves to reunite the ruptured ends of a muscle is any index of the physiological efficiency of that muscle.

With this we have disposed of the apparent differences between parenchymatous nephritis and what is called chronic interstitial nephritis.

While infections of the kidney are not ordinarily considered under the nephritides, they might as well be, for the result is the same, of course, whether the function of the kidney is impaired because toxins are carried into it by the blood stream or they are manufactured on the spot by micro-organisms present in the kidney. *The infections may give rise to either a generalized or focal type of nephritis.* If tubercle bacilli, for example, or some of the pus formers are sown into a kidney, patches of nephritis result which give rise to albumin and casts in the urine in proportion to the amount of kidney involved. If sufficient healthy tissue remains between these patches the total urinary output need not be much changed. On the other hand, if the involved patches increase in size or become so numerous as to take up the major portion of each kidney, then albumin and casts must increase and urinary secretion diminish even to the point of complete suppression perhaps. If destruction of kidney tissue results with replacement by scar tissue these infectious cases also yield secondarily contracted kidneys (chronic interstitial nephritis).

Let us complete this discussion by referring once more to Figs. 157 and 158. Under *b* of Fig. 157 is represented the atrophic remains of a healthy kidney which is called, morphologically, chronic interstitial nephritis. Such a kidney is, of course, as subject to attack by any of the causes which may underlie a generalized parenchymatous nephritis as is a normal kidney. When this occurs the normal or "increased" urinary output so often observed in the morphologically chronic interstitial nephritides gives way to a diminished one with many casts and much albumin. This is frequently *the terminal picture in the chronic interstitial types of nephritis found associated with vascular disease* and its accompanying cardiac hypertrophy and high blood pressure. The chronic interstitial nephritis is produced as already described.

But while the patient is living on his remnants of kidney, his heart muscle begins to fail or the sclerosis of the main arteries leading into the kidney reaches a fatal limit, and subject to the inadequate blood supply resulting from such the remaining kidney cells die—the "small red kidney" (Fig. 157, *b*) passes over into the "small gray" one (Fig. 158, *b*).

We shall find much evidence to support these simple views as we proceed. What will strike my readers at this time as the most obvious shortcoming in my insistence that the chronic interstitial types are also but parenchymatous nephritides, is my ignoring of the fact that with the frankly parenchymatous types we are likely to find associated a generalized œdema, while with some of the recognized types of chronic interstitial nephritis there goes no œdema, but an increased blood pressure and cardiac hypertrophy. I am ignoring these things only temporarily, however. But even here let me point out what will be proved later, that these signs, while likely to be associated with these types of nephritis, are *not secondary to the kidney disease* as generally taught, but due to entirely different causes.[1]

Let us now discuss the morphological changes observed in the nephritic kidney *seriatim*. The pathologist accepts the following as characteristic of the parenchymatous lesions whether they involve patches or the whole of a kidney. For their recognition no elaborate histological technique is at all necessary.

1. An increase in the size of the involved portions of the kidney, traceable on the examination of fresh, unfixed and unstained cells, back to an increase in the size of the individual cells and tissues composing the kidney.

2. A loss of the normal color of parts or all of the kidney which assume a less glistening, drier and more opaque (boiled) look. On microscopic examination this change is found to be associated with the appearance of granular substances in the cells of the affected portions of the kidney. This change in color, taken in conjunction with the increase in the size of the kidney, constitutes the "cloudy swelling" of the pathologists.

3. The appearance of blood corpuscles extravascularly. They may be found in the tissues of the kidney itself, or in the spaces about the glomerular tufts and in the uriniferous tubules.

4. Evidences of a falling apart of the kidney as a whole and

[1] See page 614.

of a disintegration of the individual cells of the kidney. Under this heading are grouped not only the gross destructive lesions observed in the kidney, such as the rupture of capillary tufts, but the separation of individual and groups of cells from their attachments in the glomeruli, BOWMAN'S capsule and the uriniferous tubules (formation of casts).

This catalog of morphological changes holds both for the acute parenchymatous nephritides and for the chronic forms. The chronic show all the changes of the acute with certain others added to them, notably a "fatty degeneration," and the development of a certain amount of scar tissue. As the last two take us into fields not immediately connected with our problem of nephritis, we shall not discuss them in detail.[1]

3. The Changes in the Size and in the Color of the Kidney in Nephritis (Cloudy Swelling)[2]

§ 1

While we shall later find ourselves compelled to discuss these two changes in the kidney separately, we will first take them up together because it is in this form, under the caption of *cloudy swelling*, that they have been chiefly discussed by the pathologists.

As is familiarly known, we are indebted to RUDOLPH VIRCHOW not alone for a first clean-cut description of this cloudy swelling as it occurs in the kidney (and other parenchymatous organs), but for a first attempt to analyze its nature. VIRCHOW held cloudy swelling to be "a kind of acute hypertrophy with tendency to degeneration," a phrase which has found its way into even our most modern text-books of pathology. But while such a phrase still serves many as a satisfactory characterization of the condition from a biological standpoint, it means nothing, of course, from the standpoint of its physico-chemical analysis. Toward the physico-chemical analysis of cloudy swelling VIRCHOW contributed the important suggestion that the cause of the granule formation in the cells is due to a change in their albuminous

[1] For a detailed study of fatty degeneration which has appeared since this paragraph was written see MARTIN H. FISCHER and MARIAN O. HOOKER: Fats and Fatty Degeneration, New York (1917); or Science, **43**, 468 (1916); Kolloid-Zeitschr., **18**, 129 (1916); ibid., **18**, 242 (1916).

[2] MARTIN H. FISCHER: Kolloid-Zeitschr., **8**, 159 (1911).

constitution. He based this conclusion upon the fact that the granules are soluble in acids and alkalies, and not in ether, thereby distinguishing them from fat deposits in the cells (fatty degeneration) which at times mimic in general appearance cells affected by cloudy swelling. For the increase in the size of the cells VIRCHOW gave only the biological explanation of an "increased irritation" of the affected cells, caused, for example, by the products of an infectious disease, in consequence of which they were made to take up "excessive amounts of nutrient material."

That cloudy swelling represents a change in the albuminous constitution of the cell seems never to have been questioned. EDUARD RINDFLEISCH[1] accepted this belief and, moreover, expressed himself of the opinion that cloudy swelling was "passive" in its nature and due to "a kind of corrosive action in consequence of which the albuminous matters, held in solution by the protoplasm, undergo coagulation and become visible as minute granules." In 1882 JULIUS COHNHEIM[2] subjected VIRCHOW's teachings to a rigorous critique. That the process of cloudy swelling involved the albuminous constituents of the cell he did not question, but he perpetuated a conclusion (erroneous as we shall see) of VIRCHOW, when he wrote: "Of course we must deal here with a protein that is different from that which is normally present in the cell protoplasm . . . as we could not otherwise account for the optical difference." But COHNHEIM, too, expressed the possibility of cloudy swelling representing "a spontaneous precipitation in solid form, or the coagulation of a previously fluid protein." What underlies such a change in the albuminous constitution of the cell, he did not attempt to say, but he showed conclusively that the causes proposed by earlier writers were questionable if not entirely inadequate. Thus he showed that the fever accompanying the various infections liable to be accompanied by a cloudy swelling could not by itself be the cause of the change, by calling attention to the well-known fact that cloudy swelling may be absent in cases that have run a high fever, or present in conditions not associated with an abnormal rise in temperature.

[1] EDUARD RINDFLEISCH: Pathological Histology, translated by BAXTER, 30, London (1872).

[2] JULIUS COHNHEIM: Allgemeine Pathologie, 2d Ed., **1**, 662; **2**, 570, Berlin (1882).

In such a half-hypothetical state did the subject of cloudy swelling remain until 1901, for in spite of various discussions of the subject, no clear-cut advance was made either toward defining more precisely what cloudy swelling is, nor yet in discovering a something common to all conditions associated with cloudy swelling, which might justly be regarded as its fundamental "cause." At this time H. J. HAMBURGER[1] reported a series of observations on isolated liver, kidney and spleen cells which served to establish more firmly what can justly be regarded as little more than lucky speculation on the part of the earlier writers. HAMBURGER applied to these cells observations previously made on red and white blood corpuscles. In a study of the latter he had found that various acids, including carbonic acid, bring about an exchange of substances, including water, between the red and white blood corpuscles and the serum in which they are contained. Under the influence of acids all these cells take up water from their surroundings. He paralleled this with the findings of previous observers that, in fevers of the most varied origins, acids are produced and the "alkalinity" of the blood is reduced, and so concluded that in this acid production resided the cause for the *enlargement* of the cells in cloudy swelling. He debates why acids bring about the enlargement and concludes that changes leading in the aggregate to an increase in the osmotic pressure of the cell contents are mainly responsible. HAMBURGER then points out that the white opaque *appearance* of isolated kidney, liver and spleen cells exposed to dilute acids is identical with that of cells affected with cloudy swelling and discovered postmortem. Cells treated with an acid are studded with granules, as are the cells showing a cloudy swelling that are found postmortem, and to prove that the granules are similar in character in both, and represent protein precipitates, he calls attention to the fact that the granules which he had made appear through a weak acid dissolved again as the acid concentration was increased. HAMBURGER found an analog of the production of the granules in the isolated parenchyma cells in the precipitation of protein from a diluted blood serum when an acid is added to this.

[1] H. J. HAMBURGER: Osmotischer Druck und Ionenlehre, **3**, 49, Wiesbaden (1904), where references to his earlier articles may be found. See also KARL LANDSTEINER: Ziegler's Beiträge, **33**, 237 (1903).

The first great value of HAMBURGER's studies resides in the fact that he has detailed experiments which show that all the necessary elements for cloudy swelling reside in the parenchymatous cells themselves, and that he has pointed out that what is added through an infectious disease (or, as we might say, in order to make our contention more pointed, any condition which is capable of inducing a nephritis) may be nothing more than a little acid. This simple reasoning of HAMBURGER does away with the biological terminology that has so long been applied to the subject of cloudy swelling, and renders possible an attack upon the problem in the light of the simpler concepts of physics and chemistry.

Since HAMBURGER's work I know of no contributions to the subject of cloudy swelling which have either questioned the correctness of his view, that the increased absorption of water by the cell affected with cloudy swelling represents an osmotic phenomenon, nor any which have adduced further evidence in support of the protein precipitation idea of the granule formation in this condition. As the subject is intimately connected with our problem of the morphological changes occurring in nephritis, I felt that it could to advantage be restudied, especially since the acquisitions of colloid chemistry—the chemistry of the very substances of which the kidney is composed —have furnished us with data and theoretical deductions that are of immediate applicability in the analysis of this problem. By utilizing these we shall find ourselves in a position to give a simpler physico-chemical explanation for the increased water absorption by the tissues in cloudy swelling than is contained in the unsatisfactory osmotic explanation of this part of the phenomenon, and at the same time we shall learn how the clouding of the parenchymatous organs follows the same laws as the precipitation of such a simple colloid as casein. In this way we shall find a ready explanation of the first two of the morphological changes in the kidney catalogued above and characteristic of nephritis, namely, the increase in the size of the parenchymatous elements and their change in color. At the same time we shall find that both arise from the same cause, namely, the abnormal production and accumulation of acid in the kidney, which we have previously tried to show to lie at the base of all the nephritides.

§ 2

We shall first describe a series of observations on the artificial production in excised kidneys of the changes characteristic of nephritis (production of cloudy swelling) which will prove themselves of service in the further analysis of our problem. The methods employed in these experiments were the same throughout. The kidneys of healthy, freshly killed rabbits and guinea pigs were used, which after being sliced were distributed into bowls each containing 100 cc. of the necessary solutions. As it is impossible to give absolute values to the various grades of grayness and opacity observed in the different solutions, one can, in the description of the findings, only compare the appearance of a tissue in one solution with that of a similar piece in a different solution at the same time. The general conclusions from a long series of experiments may be summarized as follows:

(*a*) When slices of fresh kidney are dropped into distilled water they slowly swell and at the same time become gray. A tone of gray that is readily distinguishable from the color of the normal organ appears over the cut surface some three or four hours after being dropped into the water. This gradually increases in intensity until, twenty-four hours after the beginning of the experiment, the tissues look decidedly gray. For a day or two longer this may continue to increase in intensity, but the change from the first twenty-four hours is not very marked. As the tissue becomes gray it shows an acid reaction to litmus, and this acid production in even a small piece of tissue may be sufficiently great to impart an acid reaction to the surrounding fluid.

(*b*) The pieces of tissue swell much more rapidly if they are placed in any dilute acid instead of in distilled water. This is shown in Fig. 159. *A* has simply been protected against evaporation. *B* has lain for an hour and a half in n/333 hydrochloric acid. The two pictures represent opposite faces of the same cut through the kidney. The tissues also become gray sooner in an acid solution than in distilled water. In n/200 solutions of lactic, formic, acetic, tartaric, hydrochloric, sulphuric, or nitric acids a decided cloudiness is visible in ten minutes after immersion. This cloudiness becomes gradually more marked.

After three hours, when the control in distilled water is just showing a grayness, the slices of tissue in the dilute acids are grayer than the controls appear the following day. The various acids show some difference in the intensity of the cloudiness that they produce, but this is so much a function of their concentration and the time, that a table of their relative effectiveness cannot be given to advantage. After another two hours the tissues in all the acid solutions are intensely gray. The control in pure water is about as gray as the tissues placed in the dilute acids were after ten minutes of immersion. On the following day an ultimate degree of grayness (a typical "boiled" appearance) is shown by all the organs in the dilute acids.

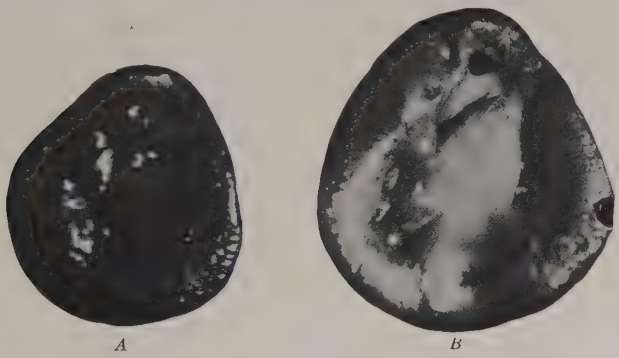


FIGURE 159.

Speaking generally, it may be said that when the effects of different concentrations of the same acid are compared, the cloudiness develops the more rapidly the greater the concentration of the acid. So far as intensity is concerned, there is, however, little difference. In the end every acid gives the tissues a boiled appearance. With different concentrations of nitric acid I found the boiled appearance after a ten-minute immersion in n/10 normal acid. In n/20 acid the same appearance was attained in an hour; in n/40, n/100 and n/500 in two to three hours.

What has been said of nitric acid holds true in general for all acids, though there are more or less specific differences with the different acids both so far as rapidity of development and intensity of the cloudy swelling is concerned. Acetic acid

is particularly interesting. With increasing concentrations of the acid there is first an increase in the rate and (in units of time) in the intensity of the cloudiness produced. If we observe closely, this is seen to be followed with increasing concentrations of acid (above n/10 acetic acid) by a stage in which the cloudiness is *less* than in lower concentrations. To see these successive changes one must observe especially the superficial portions of the tissues. A second clouding can now be obtained by changing to one of the "strong" acids (nitric, sulphuric, or hydrochloric) of the same or of a higher normality than that of the acetic acid which has brought about the disappearance of the first clouding. This change from cloudiness to clearness and back again to cloudiness, with progressive increase in the concentration of an acid, can be followed particularly well under the microscope (see (*g*) below). But even in the sections of tissue kept in the "stronger" acids can two such regions of cloudiness separated by one of clearness be discerned. I found, for example, that the marked cloudiness of slices of kidney, which had been kept for 1½ hours in concentrations of nitric acid up to n/200, disappeared when the surface of the organ was touched with the ordinary weak acetic acid of our laboratory reagents, to reappear when dilute nitric acid was substituted for it.

The cloudiness of the tissues obtained in any of the acids listed above, if developed in not too high concentrations (below n/200), can also be made to disappear if the tissues are placed in equinormal alkali solutions, or in alkali solutions of a higher concentration.

(*c*) Through the addition of various salts the development of a cloudiness in any *acid* solution can be either retarded or hastened. So far as the absorption of water is concerned, all the salts have but one effect—they decrease the amount of the swelling in the acid solution. When to n/200 hydrochloric acid enough of various potassium salts is added to make their final concentration m/20, the following is noted. After ten minutes' immersion it is plainly evident that some of the salts are accelerating the effect of the acid in producing the development of the cloudiness, while others are inhibiting it. In an hour the differences are very marked. The sulphocyanate, iodid, bromid, and nitrate all increase the cloudiness, the first

named being the most powerful in this respect. Then comes the pure acid. Following this comes the chlorid, the acetate, the tartrate, and the citrate. After three to six hours of immersion the differences are still more striking. In the solutions containing the first-mentioned salts the tissues are "boiled" in appearance. In the pure acid the grayness is well marked. The tissues in the solutions containing the chlorid and the acetate lag somewhat behind the pure acid. In the tartrate a faint film is only just visible over the surfaces of the organs. The sections in the solutions containing the citrate look perfectly normal. In fact, in the two last-named solutions the organs retain an almost normal appearance for two to three days.

Similar results are obtainable by using sodium or ammonium salts in place of the potassium salts, or lactic, formic, or nitric acid in place of the hydrochloric, except that in the latter case the absolute rate at which any degree of cloudiness is obtained is not quite the same as in hydrochloric acid.

(*d*) Various salts accelerate or retard the development of a cloudiness in sections of kidney placed in their *pure* solutions, in the same way as they accelerate or retard the development of a cloudiness if an acid is added at the same time, only the rate of development and the absolute intensity of the cloudiness attained is less in the pure salt solutions than in mixtures of these with any acid. In all salt solutions the kidney slices swell less than in pure water. These findings are to be interpreted by noting that the excised tissues become acid, so that the tissues placed in the pure salt solutions are really in the same state as the tissues described in the preceding paragraph—the tissues are really in an acid solution plus certain salts—only the concentration of acid is lower in this case than in the previously described experiments.

(*e*) Alkalies do not produce a cloudiness of kidney parenchyma in any concentration. Sodium, potassium, ammonium, and calcium hydroxids were employed in concentrations up to n/33. The superficial layers of the tissue slices "dissolve" in the hydroxids, covering the tissues with a clear, gluey mass. After two or three days the tissues lose their bright normal color, but the grayness assumed is only slight. The slices of kidney swell just as they do in acid solutions.

(*f*) The addition of any salt to the solution of an *alkali* does not lead to any cloudiness of the tissues, though it markedly reduces the tendency of the superficial layers of the tissues to go into "solution," and the swelling of the tissue fragments as a whole. I have tried without effect the chlorids, bromids, iodids, nitrates, sulphates, sulphocyanates, acetates, tartrates, and citrates of sodium, potassium, and ammonium in conjunction with the hydroxids of sodium, potassium, and ammonium. I have also tried a few strontium and barium salts with these hydroxids and calcium hydroxid, employing all in such low concentrations as to prevent the formation of precipitates, but I got no cloudiness of the immersed tissues.

(*g*) The macroscopic changes observed in the kidney when immersed in water, various acids or alkalies, in salt solutions, or these in combination, show a series of interesting parallels microscopically.

A perfectly fresh scraping from the kidney shows the cells to possess a fairly clear protoplasm in which lie but few granules. Even after the kidney cells have been kept for twenty-four hours (simply in their own moisture, and protected against evaporation by being covered) they show no change from this appearance. But as soon as water touches the cells, especially if the organ has been kept for twenty-four hours, or if they are placed in any very dilute acid, a grayish film is seen to develop macroscopically, and microscopically the cells are now found thickly studded with granules. This is the typical histological picture of the cloudy swelling described in our text-books of pathology. If now, while such cells are being observed, a little caustic soda is allowed to run under the cover slip, the cells as a whole are seen to swell, the granules to become fainter, then fewer, and finally to disappear entirely, and if enough alkali is added the whole goes into homogeneous "solution."

The granules can also be made to disappear by the addition of more acid; they form, for example, in very dilute acid, and disappear again if the concentration of this same acid is raised. Most interesting is the fact that this granular appearance can be made to come a second time by still further increasing the concentration of the acid. Acetic acid will not do this, but nitric acid will do it promptly. If strong nitric acid is used this second appearance of the granules is only a temporary affair,

for they again disappear as the whole tissue goes into "solution." With the second appearance of the granules the cells undergo a marked shrinkage from the more swollen state attained previously, but this shrinkage, like the second appearance of the granules, is also only temporary, and the cell undergoes a final enormous swelling before being "dissolved."

§ 3

How now are we to interpret these various findings, and what light do they bring us regarding the cause and the essential nature of those changes of like character, which we observe in the kidney in nephritis and which lead to the increase in its size and to the change in its color. Our first attention must be dedicated to the *increase in the size of the cells.*

H. J. Hamburger recognized clearly that the fundamental cause for the increase in the size of the cells affected with cloudy swelling lies in the production of acid in them. As we have already learned, evidences of *an abnormal production and accumulation of acid in the kidney occurs in every case of nephritis, and so we may make this circumstance, which we have already made responsible for the albuminuria, responsible for this increase in the size of the kidney also.* But how does an abnormal acid content manage to bring about the increased water absorption which leads to the increase in the size of the cells (and so of the kidney as a whole) in nephritis? Hamburger answered this question by attributing an indirect effect to the acid, whereby this was assumed to increase the osmotic concentration within the cells. The enlargement of the cells in "cloudy swelling" represents an œdema of the affected cells, and this is most easily accounted for on the basis of the colloid constitution of living matter. The serious objections that can be lodged against the widely accepted belief that cells represent osmotic systems cannot be raised against the view that the lyophilic colloids of the tissues and their state determine the quantity of water absorbed by a cell. As previously emphasized, the amount of water that such colloids (as represented by gelatin, fibrin, and serum albumin, for example) will absorb is enormously increased if any acid is present. This fact receives incidental illustration in Fig. 148. On this basis,

it is easy to parallel the absorption of water, and so the enlargement of the cells of the kidney when affected by nephritis, with the increased amount of water absorbed, say by a gelatin cube or some fibrin particles, when instead of being placed in water they are placed in a dilute acid of some kind. In the case of gelatin and fibrin, and similarly in the case of the experiments on excised kidneys, the source of the water for the increased swelling is to be found in the solutions surrounding these colloid structures; in the case of the nephritic kidney, in the blood and lymph streams passing through the organ.

There is, within certain limits, an increase in the amount of the swelling of such protein colloids as gelatin or fibrin with every increase in the concentration of the acid surrounding them. On this basis we can understand the increase in the swelling of the kidney cells with every increase in concentration of the acid up to a certain point. When a certain optimal concentration of the acid is exceeded, the colloid swells less than in weaker solutions (see Fig. 148). This furnishes a ready interpretation of the finding detailed above, that on substituting nitric acid for a weaker solution of acetic acid, kidney and liver cells are seen to shrink. Incidentally, it is worth while emphasizing that in the great rapidity with which such cells will give off and take up water, in changing from a medium of one concentration to another having a lower or a higher one, lies a powerful argument against the osmotic pressure idea of water absorption in cells. I have seen these cells pass from the swollen state, in a weak acetic acid solution, to the greatly shrunken state induced by nitric acid, and through a second swollen state into "solution" in less than two seconds. Equalizations of osmotic differences either through a movement of solvent, or of dissolved substance, do not occur with such velocity.

We may now turn to a consideration of *the changes in the color of the kidney in nephritis*, and see how these become interpretable on the basis of the fact that in this condition an abnormal amount of acid is present in the kidney.

The statements made above regarding the means by which a cloudiness can be produced in the parenchymatous cells of the kidney, or regarding its rate of development, or the means by which the intensity of such a cloudiness may be increased or decreased, have all of them parallels in the ways and means

by which protein may be precipitated from one of its "solutions," or such a precipitation be hastened or retarded. *The development of a cloudiness in the kidney cells follows most closely the solution and precipitation of such a colloid as casein.*[1]

Casein [2] is insoluble in water. It is soluble in dilute hydroxids, in which state it is electro-negative. It is in this state that we find the body proteins normally, as WOLFGANG PAULI [3] has shown. In the left-hand tube of Fig. 160 is shown the perfectly clear casein solution made by saturating an alkali (NaOH) with

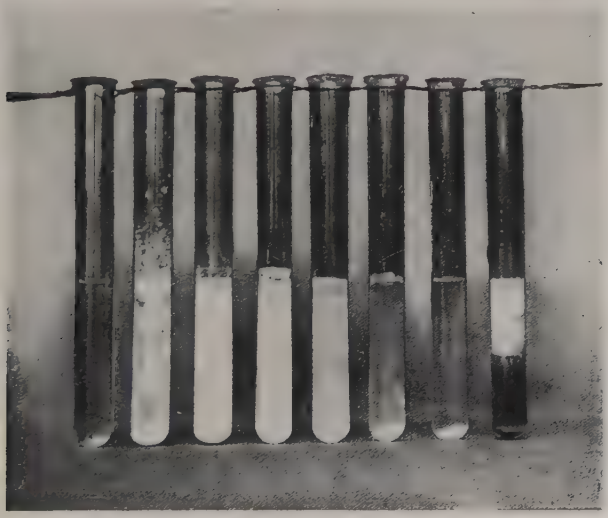


FIGURE 160.

casein. When a dilute acid is added to such an electro-negative protein, let us say to the solution of casein in any hydroxid, a precipitate of the casein is thrown down, as shown in the second tube. A similar precipitation of an electro-negative colloid

[1] This term is used in HAMMARSTEN's sense and corresponds therefore with the caseinogen of HALLIBURTON.

[2] For a discussion of the general properties of casein see O. HAMMARSTEN: Physiological Chemistry, translated by MANDEL, New York (1914); E. LAQUEUR and O. SACKUR: Hofmeister's Beiträge, **3**, 193 (1903); W. A. OSBORNE: Jour. Physiol., **27**, 398 (1901); T. B. ROBERTSON: Jour. Biol. Chem., **2**, 317 (1907); L. L. VAN SLYKE and E. B. HART: Am. Chem. Jour., **33**, 461 (1905).

[3] WOLFGANG PAULI: Naturwissensch. Rundschau, **21**, 3 (1906).

occurs when our sections of kidney are immersed in any dilute acid. The development of a cloudiness in tissues immersed in water is also to be regarded as a precipitation through a dilute acid, only in this case the tissues themselves produce the acid. Similar conditions hold in nephritis, when, in consequence of the abnormal acid content of the kidney, some of the protein constituents of the cells composing this organ are precipitated. As we have already found this same acid to be responsible for an increased swelling of the tissue colloids, it is easy to see how from the two there results, when water is available, the picture we designate " cloudy swelling."

But our analogy goes further than this. If we continue to add acid to the reaction mixture in which our casein began to be precipitated, the precipitate becomes heavier (as in the third and fourth tubes of Fig. 160), but soon, with still further addition of acid, the casein begins to go back into solution. This is evident in tubes five, six, and seven, the last of which is again entirely clear (the white spot at the bottom of the tube in the photograph being a highlight). This is what we observe in the kidney cells when we note the cloudiness produced in a weak solution of any acid, or that found in the nephritic kidney on autopsy, to disappear on applying a stronger solution of the acid (say acetic acid) to the kidney. This macroscopic change has its parallel in the microscopic disappearance of existing granules in a cell, the seat of a cloudy swelling (found either postmortem or induced artificially), when acetic acid is run under the coverslip. But the casein thus redissolved in such an acid as acetic acid can be precipitated a second time if strong nitric (or hydrochloric or sulphuric) acid is allowed to flow into the test-tube as shown in the tube on the extreme right of Fig. 160. If the protein is not present in excessive amounts, this second precipitate also disappears—we say it goes into solution in the excess of the nitric acid. It is not difficult to see that this is entirely analogous to the reappearance of granules in the kidney cells, with subsequent total solution of the affected cells, on the addition of nitric acid for example, to cells in which a previous set of granules has been made to disappear by the addition of acetic acid.

Equinormal solutions of different acids are not equally effective in producing a precipitation of casein; neither are they

equally effective in producing the cloudiness of cloudy swelling. In low concentrations certain salts favor the precipitation of casein by dilute acids while others hinder this. The sulphocyanates and iodides quickly precipitate casein from an acid solution in heavy curds. Equimolar solutions of the bromids, nitrates, and chlorids produce only an opalescence, while in citrates the casein remains in solution. When arranged according to the intensity with which these acid radicals favor the development of a cloudiness in the kidney the order is the same. Various basic radicals, in the dilute solutions in which they have to be used to prevent their precipitation as hydroxids, do not influence the precipitation of casein. Neither do they affect the development of cell cloudiness.

Kidney cells also follow the behavior of casein toward alkalies. All the alkalies make casein go into solution and, similarly, the alkalies do not produce any clouding in kidney cells.[1] Casein is not precipitated in alkaline solution by the addition of any of the ordinary salts. Neither is a cloudiness produced when any salts are added to slices of liver or kidney immersed in a dilute alkali.

Point for point the analogy between the precipitation of casein and the artificial development of a cloudiness in kidney cells seems therefore to be complete, and since there exists no discoverable difference between the changes thus artificially induced in excised kidneys and those which nature produces for us in this same organ in nephritis, nor yet in the conditions leading to these changes in either case, we would seem to be justified in considering all these changes as in essence the same, and as caused fundamentally by the same circumstances.

As this process of cloudy swelling represents a series of changes in the state of the cell colloids, it is clear that the employment of any methods in its study—such as fixing agents and various stains—which in themselves are capable of producing changes in the state of cell colloids, should be excluded. Nevertheless, to meet the possible objection that what has been described in these pages as cloudy swelling might really not be identical with this change as observed on the autopsy table, our

[1] The slight grayness developed by slices of kidney, kept for several days in a dilute alkali, has its parallel in the turbidness which we find developed in alkaline solutions of casein, when these are kept for longer periods of time.

pathologist, PAUL G. WOOLLEY, generously offered to examine by approved histological methods the tissues in which I had produced cloudy swelling artificially. He reports that the pictures obtained are identical with the most extreme grades of cloudy swelling that are encountered pathologically.

In concluding these paragraphs we have to answer the final question of *the relation of the swelling of the kidney cells to the clouding in them.* On the basis of the fundamental work of WOLFGANG PAULI[1] and his coworkers, HANS HANDOVSKY and KARL SCHORR, this is easily done. These investigators have emphasized that the swelling and solution of a protein colloid are the antitheses of the loss of water by and the precipitation (dehydration) of the same colloid,—that the two processes are therefore mutually exclusive. It follows from this that the swelling of the cells in a parenchymatous nephritis, and the development of a cloudiness in them, cannot possibly involve but one colloid —in other words, at least two must be involved. The conditions which permit the one of these to imbibe water and so to lead to an increase in the size of the cell are of such a character as to lead to the precipitation of another, and so to the cloudiness. WOLFGANG PAULI kindly advised me to test out this idea in a model made by pouring a solution of casein (prepared by saturating sodium hydroxid with casein) into a concentrated, carefully washed gelatin (20 per cent) and allowing the whole to stiffen. When plates are cut from such a mixture they swell (absorption of water by the gelatin) and become cloudy (precipitation of casein) under the same conditions (presence of acids and various salts) as were found above to lead to a " cloudy swelling " in slices of kidney.

[1] WO. PAULI: Kolloid-Zeitschr., **7**, 241 (1910); PAULI and H. HANDOVSKY: Biochem. Zeitschr., **18**, 240 (1909), **24**, 239 (1910); H. HANDOVSKY: Kolloid-Zeitschr., **7**, 183, 167 (1910); Fortschritte in der Kolloidchemie der Eiweisskörper, Dresden (1911); KARL SCHORR: Cited by PAULI and HANDOVSKY.

4. The Bleeding into and from the Kidney in Nephritis (Hemorrhage by Diapedesis)

The blood that appears in the urine in some cases of nephritis is of purely traumatic origin, in other words, capillaries or larger blood vessels are ruptured and the blood escapes. In large part, however, pathologists hold that blood corpuscles get from the capillaries into the urine by a process of *diapedesis*. Through diapedesis are also explained many of the hemorrhages into the kidney substance itself. As such bleeding does not occur from the normal kidney we become interested in its mechanism, and it becomes a part of our problem to discover why in nephritis such a process which occurs also in other pathological states should be especially prone to appear.

We still lack a satisfactory explanation of the mechanism of diapedesis. Our present teachings continue to partake of the views of VON RECKLINGHAUSEN and JULIUS ARNOLD, who held that holes (so-called stomata) exist in the capillaries, and that through these the red blood corpuscles escape in conditions associated with a bleeding by diapedesis. But such a conception, as JULIUS COHNHEIM pointed out years ago, is grossly incorrect, for what escapes from the blood is not the whole blood, but only the red blood corpuscles, and it is inconceivable how holes which would permit the passage of the cellular elements of the blood through them should hold back the liquid portion of the blood. COHNHEIM believed diapedesis to be dependent upon changes in the blood vessel walls whereby these became abnormally permeable, after which he held the blood pressure to be able to force the red blood corpuscles through them. How such an abnormal permeability was brought about he declared himself unable to explain.

Hemorrhage by diapedesis, while discussed by us because present in some forms of nephritis, is really, of course, a widely distributed pathological phenomenon. As is familiarly known, it occurs in any well-marked passive congestion, produced, for example, by ligation of the veins of any of the parenchymatous organs, of the mesenteric veins, or of those coming from the leg or the ear of a rabbit or dog. But it occurs also after ligation of the arterial blood supply to a part,[1] and I have observed it in

[1] See page 269.

the entire absence of any circulation in the legs of frogs so ligated as to close both arteries and veins, and kept in a little water. Hemorrhage by diapedesis occurs also in conjunction with the acuter forms of inflammation no matter how induced.

These remarks make it clear that blood pressure, which might at first sight be thought to be of some importance in squeezing the red blood corpuscles out of the blood vessels into the surrounding tissues, cannot be of great importance in this regard, for diapedesis occurs in conditions associated with a decrease in the blood pressure, or, as just pointed out, even in its entire absence. What is present in all the conditions noted is such a disturbance in the circulation as to lead to a state of lack of oxygen in the tissues, and, we have to repeat, an abnormal production and accumulation of acids in the affected regions. And this is what we have in the kidney in nephritis. But how does this now lead to the diapedesis? The answer is not hard to find.

We have already called attention to the well-known fact that the cells of the living organism represent in the main a mixture of several so-called lyophilic colloids. Under normal circumstances in the body these are in a swollen state that is similar to that assumed by fibrin or gelatin when placed in water. If a little acid is introduced into such a colloid the absorption of water by it is enormously increased, and as we have already pointed out, this is what happens when acid is introduced into the kidney (or into the tissues of the other parenchymatous organs, the intestine, the leg or the ear), in other words, an "œdema" develops. But this increased absorption of water makes the tissue *softer* (or, to put it more technically, its internal friction is decreased and its surface tension is changed) and now the red blood corpuscle which lies in contact with its surface is no longer held out by the surface layer of the tissue colloids (the blood vessel wall), but penetrates this—is really "swallowed" by the tissue. The increased fluidity of the kidney tissues, after these have been treated with a little acid in the presence of water, is readily observable under the microscope. The cells can be pushed about and molded on slight pressure in a most striking way.

What makes the red blood corpuscle move through the tissues are inequalities in the stresses present in the tissue colloids. By

a process, the reverse of that described, the tissue which has once swallowed a red blood corpuscle may again get rid of it, though in practice such a result is hardly to be expected, for after a softened tissue that has swallowed some red blood corpuscles has a more normal circulation restored to it, it is likely to lose its excess of acid, and therefore its water, so rapidly that the red blood corpuscles remain behind entangled in the tissues. As a matter of fact, we know that red blood corpuscles which have escaped unto the tissues are usually absorbed indirectly after they have disintegrated.

What we have said here regarding the red blood corpuscles holds also, of course, for the *white blood corpuscles*, only these possess in addition independent powers of movement which are *lacking* to the red blood corpuscles.[1] More strictly in the class with the red blood corpuscles belong *the bacteria* which we know may reach the kidney from any part of the body and pass through the kidney substance into the urine.

Briefly formulated, the problem of how in nephritis the red blood corpuscles pass into the tissues of the kidney or through these out into the urine, or the problem of how white blood corpuscles or bacteria do this comes to be the problem of how one colloid body may pass through another, and of the laws that govern such a passage. No holes are necessary in order that one colloid may pass through another, and such a passage is accomplished without one colloid losing its identity in the other or leaving behind it any evidence of its passage.

The matter can be prettily illustrated by letting a mercury drop or solid metals (iron fragments or shot, or these covered with colloid material as agar-agar or collodion), under the influence of gravity, move in all directions through a solidified gelatin. The mercury is particularly suitable, for, while not a colloid, it has the "liquid" character possessed by the red and white corpuscles. In the body the migration of the blood corpuscles (or metal fragments, etc.) does not, of course, occur under the

[1] In the discussion of the migration of white blood corpuscles in inflammation (chemotaxis) most emphasis is always laid upon the changes that the white blood corpuscles themselves are believed to suffer (for example, changes in surface tension), which result in their movement toward the inflammatory center. This is only half the problem. The changes in the tissues themselves (changes in viscosity, for example), produced through the action of the excitant of the inflammation, also play a rôle.

influence of gravity, but in consequence of inequalities in the pressure exerted upon the surface of these elements, occasioned through inequalities in the stresses present in the tissues (brought about in turn through local changes in the water content of the lyophilic colloids comprising the tissues). And as the question of whether a mercury drop will enter a solidified gelatin, and the rate at which it will move about in this are matters that have to do with the surface tension relationships that exist between the mercury and the gelatin, and the viscosity of the gelatin (in its turn, affected by concentration, temperature, acids, bases and salts), so these same factors play a rôle in diapedesis as observed in the living organism.

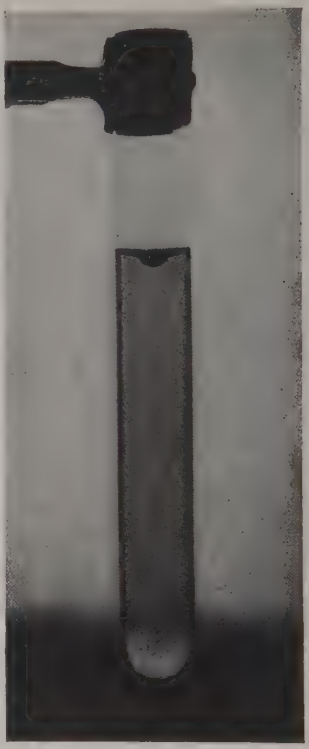


FIGURE 161.

In Fig. 161 is shown how a mercury drop is unable to penetrate a stiffened gelatin (3 per cent) at room temperature. It may be rolled about on the surface of the gelatin without entering it. If the experiment is repeated at the same temperature, with a stiffened gelatin of a somewhat lower concentration, the mercury drop enters it and falls slowly to the bottom (Fig. 162, *a*, *b*, *c*). By turning the tube about (Fig. 163), the mercury drop moves in all directions through the stiff gelatin in which, of course, no holes exist, and in which none remain after the mercury has passed.[1]

The essential change in the gelatin, which makes such penetrability possible in this experiment, was induced through regu-

[1] It is this property of colloids which explains why small wounds made in the living animal close immediately. The property of colloids, which gives them such great interest biologically, is the fact that they combine in one the properties of liquids (surface tension, viscosity, diffusion of dissolved particles) with the properties of solids (maintenance of form).

lation of the concentration. A similar change can be induced by raising the temperature somewhat (not to the point of melting the gelatin, of course) or, *in the presence of water*, by adding a little acid. This approximates most closely the change that occurs in the body when in passive congestion, for example, a

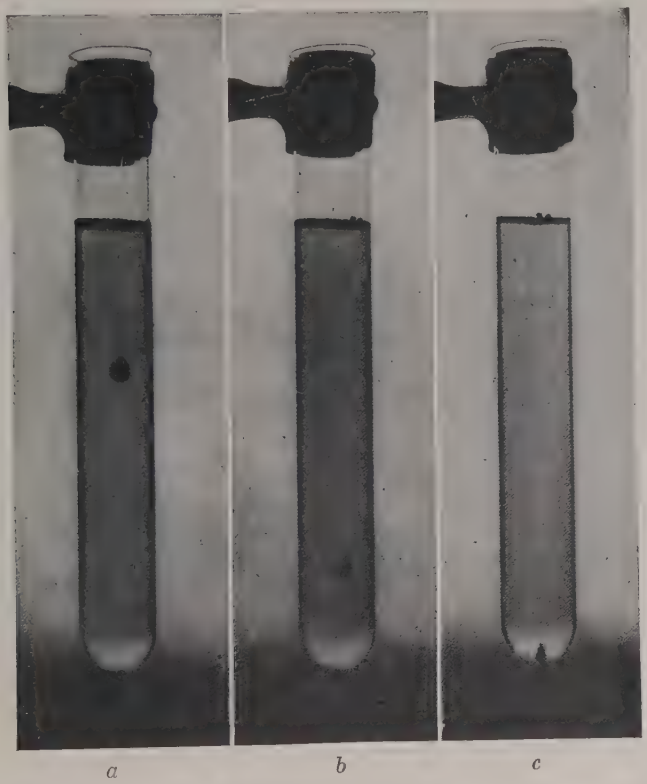


FIGURE 162.

diapedesis into the œdematous tissues is noted. What happens under such circumstances can also be mimicked with some gelatin cakes and a few mercury drops. If one gelatin cake is placed in water, another in a dilute acid, the one in acid undergoes a swelling which after a time reaches a stage which readily admits of the passage of a mercury drop, while the control in water will not.

5. On the Origin and the Different Types of Tube Casts

We have now to discuss how the abnormal acid content of the kidney in nephritis leads to the formation of casts. In this section we shall also learn how the various types of casts that are discovered in the urine in nephritis bear a simple relationship to each other; how, in fact, it is possible to convert one type of cast into another, and back again if we so choose, under the conditions found in the kidney and in the urine in nephritis.

FIGURE 163.

What must be the effect of the abnormal production or accumulation of acid in the kidney, so far as this problem of casts is concerned, may be determined in any one or all of several ways. We may simply leave the normal kidney, freshly removed from the body, to itself, protect it against evaporation, and study the effects of the postmortem development of acid in it. Or, we may slice the kidney into pieces and place them in water, or, finally, we may place such slices directly into slightly acidified water. The kidneys of guinea pigs and rabbits furnish excellent material, and it is on these that the following observations were made.

When we take a *fresh kidney* that has been cut across and squeeze it gently, we only see a little blood ooze from the blood vessels. If we scrape the surface and put a little of the scrapings on a slide, we find little more than some red blood corpuscles mixed with some granular material. In other words, it is difficult to obtain any kidney parenchyma cells—they do not separate easily from their attachments. The same kidney, preserved for several days, presents a different appearance. The surface may not be so glistening when cut, and on squeezing the organ, turbid points arise over the surface of the kidney which, when examined microscopically, are seen to be made up of epithelial cells which have loosened from the kidney tubules. These

may be single, or joined together in groups, and with them are again found the red blood cells and the granular detritus that was observed in a scraping from the perfectly fresh kidney.

A somewhat different picture is presented by the sections of kidney that are placed in water. Such tissues become gray more quickly than the tissues that do not come in contact with water, and develop an opaque appearance. The normal kidney markings gradually become obscured, and the tissues as a whole are seen to swell somewhat. The whole makes up the typical picture of that which the pathologists call cloudy swelling, and the nature of which was discussed in a foregoing section. The scraping from the surface of such a gray kidney shows a large number of free epithelial cells, which one has no difficulty in recognizing as coming from glomerular tufts and from the uriniferous tubules. In making the scraping one notices, moreover, that while vigorous scraping yielded little or nothing when applied to the healthy kidney, it is no trick at all to get an abundant amount of material from the surface of a kidney that has lain in water for a day or two. One notices, moreover, that the numerous epithelial cells are swollen and studded with granules. But beside the individual epithelial cells one notices groups of these, and then casts with rounded ends. One has no difficulty in recognizing these as duplicates of the epithelial casts found in the urine in certain types of nephritis.

But the most striking picture is that presented by the sections of kidney thrown into a weak acid of some kind. In this the cloudy swelling of the slices of kidneys already described occurs very rapidly. *A gentle scraping from the surface of a kidney slice, treated with dilute acid* (n/500 lactic, for example), *shows in several hours after immersion a granular detritus, separate epithelial cells, groups of epithelial cells and casts of various kinds* (Figs. 164 and 165). *When the kidney is simply gently squeezed and its surface touched to a slide, and this is then examined microscopically, one cannot escape the impression that he is examining a centrifuged urinary specimen from a case of acute nephritis. The epithelial cells, the epithelial casts, the granular casts are all there. One misses only the hyaline cast, but this can be promptly obtained by simply adding a little stronger acid to the specimen under the microscope, when the granular casts are seen to lose their*

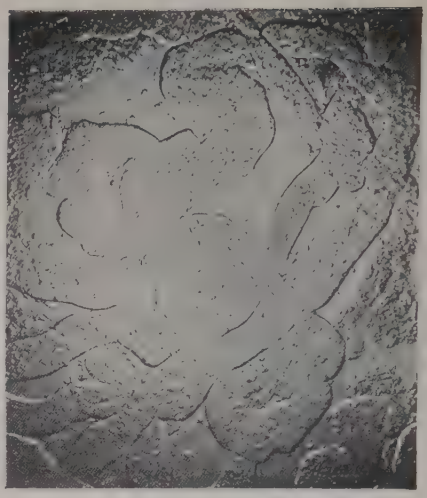


FIGURE 164.

granules, swell somewhat more decidedly and become difficultly visible. Scattered nuclei may stick to the casts, but if enough acid is added, these too, go, so that only the greatly swollen, entirely hyaline "cylindroids" of some authors remain. Or, we can assure ourselves of a generous yield of hyaline casts and cylindroids from the start if we simply increase the acid concentration into which kidney slices are dropped or prolong their residence in the solution.

We can convert the granular casts into hyaline ones quite as easily through the addition of an *alkali* as through the addition of an acid, and if the kidney slices are from the first dropped into a dilute alkali, only hyaline casts are obtained. The hyaline casts produced through the acids can be converted back into granular casts, if we wish, by simply running a little salt under the cover slip. A sulphocyanate is particularly good for this purpose, but if we wish to use a salt that is more "physiological" in nature,

FIGURE 165.

sodium nitrate or sodium chlorid will do. The hyaline casts produced through alkalies can also be converted into granular ones, though to accomplish this they must be treated with an equinormal acid. Why all these transformations are possible is, of course, readily intelligible when the experiments on cloudy swelling as detailed in the previous sections are recalled.

In Fig. 166 is shown the appearance of a gentle scraping taken from a slice of kidney that had lain in water for several hours.

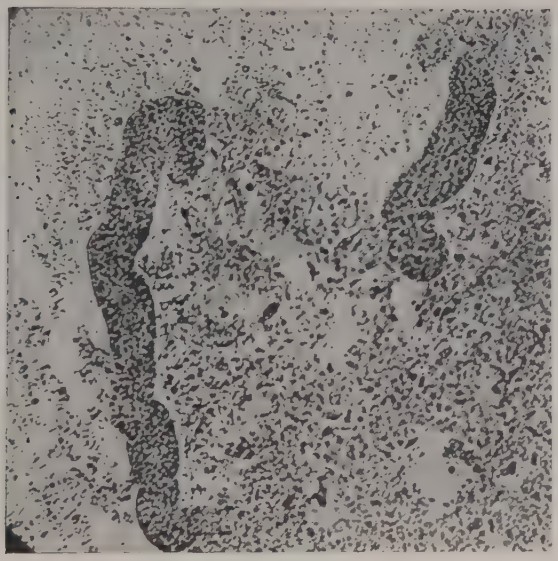
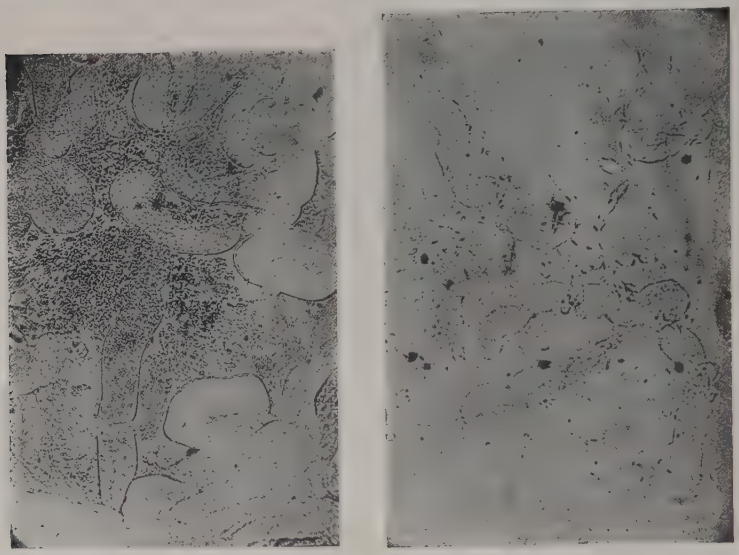


FIGURE 166.

A granular cell detritus and isolated casts characterize such a specimen. Nuclear fragments are prominent, and the epithelial cells may in places still be made out. The cells are granular. In Fig. 167, *a*, is shown a scraping similarly prepared from a slice of kidney that had lain in n/200 acetic acid for three hours. The cast formation (falling apart of the kidney) is a far more prominent feature. In the cast occupying the central point in the photomicrograph remnants of an epithelial structure are still present. In the casts lying above this all evidences of nuclear structure have disappeared. They are filled with fine granules.

When these casts were treated with a stronger solution of acetic acid they became hyaline, as shown in Fig. 167, *b*.[1]

It is clear, therefore, that under the influence of a little acid the kidney drops apart into its morphological elements. While these are firmly cemented together in the healthy kidney (as witness the attempt to obtain them by scraping the surface of the kidney with a knife), they are separated with the greatest ease after the kidney has lain in acid for a while. The answer



a *b*

FIGURE 167.

to why the kidney falls apart as it does under the influence of acid it is needless to discuss, but the view that some of the (colloid) " cement substances " are more easily " soluble " or more easily " digested " in weak acids than other portions of the kidney at once suggests itself. Such a view finds support in our previous considerations of albuminuria and in the fact, easily observed in

[1] Casts lose their granules and appear hyaline to ordinary microscopic vision before they become hyaline *photographically*. This is easily explained by the optical behavior of colloids. As WOLFGANG OSTWALD has emphasized, the ultraviolet rays affecting the photographic plate are still refracted (and the picture appears granular) by particles too small to change the path of the longer rays of ordinary white light.

these experiments, that the solutions in which the kidney slices lie, come to contain, with time, progressively larger amounts of albumin. That some constituents of the kidney (or of any other organ) are more readily soluble in an acid than are others, is clearly enough evident under the microscope. The nuclei of the cells still retain their outlines, for example, in concentrations of acid in which the protoplasm generally has become entirely hyaline. The action of the acid could be aided and abetted, of course, by the various substances which in their action on the body colloids act like acids, including the enzymes.

What is important to us, from the standpoint of the theory of nephritis, is *the way in which the kidney falls apart. The epithelial cells tend to stick together while they separate in mass from their supporting membrane. This marks the origin of the urinary cast* which, in clinical cases, is washed down into the bladder by the force of the secreted urine.

These simple facts regarding the origin of casts, and the conditions under which the one type may be converted into another, are not without clinical significance. In treatises on medicine and in works on clinical diagnosis much has been said, not only regarding the importance of the appearance of casts in the urine, but of the significance of the different kinds of casts. It seems to me that the experiments just detailed urge caution upon one in drawing too sweeping conclusions from such data. So far as mere numbers of casts are concerned, it requires no special emphasis to realize that great numbers of casts present in the urine at one time, while indicative of a more extensive involvement of the kidney parenchyma at that time may not be as significant as a lesser number present over longer periods of time. The aggregate destruction may in the latter case, of course, be much greater than in the former (a condition further modified in the living organism by the rate and quantity of the regeneration occurring in the kidney).

In judging of the meaning of the character of the cast, whether epithelial, granular, or hyaline, one must be exceedingly careful. We have seen that the epithelial cast is readily convertible into either the granular or the hyaline, depending upon how much acid is present and the length of time that it is allowed to act; and the hyaline, we have seen, can be reconverted into the granular. The thought might suggest itself that we use

the nature of the cast as an index of the acid concentration in the kidney and so as a measure of the intensity of the nephritis. But this may not be done, for we know from autopsy findings that a nephritis need not affect all the parts of a kidney equally, or at the same time, and the urine represents the mixed product of the whole kidney. Moreover, the urine itself varies so in composition under different (physiological) circumstances that it may alter the character of the cast in its passage through the ureter and bladder, no matter what its nature when it left the kidney. A highly acid urine would on the whole tend to yield granular or, if sufficiently high, hyaline casts. An alkaline urine would tend to yield only hyaline casts. On the other hand, the salts of the urine would tend to counteract the acid and make the casts not only smaller (loss of water by the colloid) but more granular (precipitation of the colloid). One can easily satisfy himself of these facts by providing himself with casts from a clinical case of acute nephritis, or from such kidneys as I have described, and examining them under the microscope, while a little acid, or this in conjunction with various salts, is allowed to run under the coverslips of the preparations.

In concluding this section it is well to revert for a moment to the question of albuminuria. It is possible to test the idea that albuminuria results from a "solution" of the proteins of the kidney under the influence of an acid in these experiments on the formation of casts. If we take a perfectly fresh kidney from either a rabbit or a guinea pig, cut it into several slices, and wash the pieces a few times in water or a "physiological" 0.9 per cent NaCl solution, so as to get rid of the blood, we find thereafter that the wash water gives little or no reaction for albumin. But if we permit the pieces of kidney to lie in the wash water until next day, we have no difficulty in getting the albumin reaction. Still more rapidly do we get it if we immerse the washed slices of kidney from the start in a weak acid solution. If we pipette off the sediment found about the kidney pieces and examine this under the microscope, we find at the same time various kinds of casts. But the albumin is not simply due to these, for we continue to get a marked albumin reaction after careful filtration.

VII

SOME RESPONSES TO CRITICISM

There has been much that is foolish written against the simple conclusions outlined in the foregoing pages according to which the tissues of living organisms owe their water holding power to the fact that they contain hydrophilic colloids, that they become œdematous whenever such water-holding power is increased (as through the presence of abnormally high amounts of acids) and that in the "solution" or liquefaction of such colloids (also under the influence of acids and similarly acting substances) is to be found the essential mechanism of albuminuria. Many of these criticisms rest upon a misreading or an actual violation of what I have written and to such it is mere futility to respond. It is the purpose of these paragraphs to revert to the oft-repeated objection that an abnormal production or accumulation of acids in a cell, tissue or organ can not be a potent cause of œdema, albuminuria, etc., because the tissues contain phosphates or other "buffer" salts which have the power of taking up considerable amounts of either acid or alkali without change in "hydrogen ion acidity." [1] Aside from the fact, often pointed out before, that such buffer action is not unlimited in amount, that there is a vast difference between our constantly reiterated "acid content" of tissues and their hydrogen ion concentration, that the physiological action of even pure acids nowhere parallels their electrolytic dissociation, and that even with extreme variations in acid content there may be little change in hydration capacity if various neutral salts are present, the following data show that *from a given low point, even in the presence of such "buffer" salts, there is a progressive increase in water absorption by various proteins and a progressive tendency to liquefy or go into solution with every increase in the acid or alkali content of the mixture.*

1. On the Swelling of Gelatin in Polybasic Acids and their Salts [2]

Dried gelatin discs prepared in the accepted fashion[3] served as the material upon which to test out the effects of different poly-

[1] See, for example, Max Koppel: Deut. Arch. klin. Med., **112**, 594 (1913); L. J. Henderson, W. W. Palmer and L. H. Newburgh: Jour. Pharm. Exp. Therap., **5**, 449 (1914).

[2] Martin H. Fischer and Marian O. Hooker: Science, **46**, 189 (1917); Jour. Am. Chem. Soc., **40**, 272 (1918.

[3] See page 75.

basic acids and their salts. For the polybasic acids we chose phosphoric and carbonic because of their importance in the animal

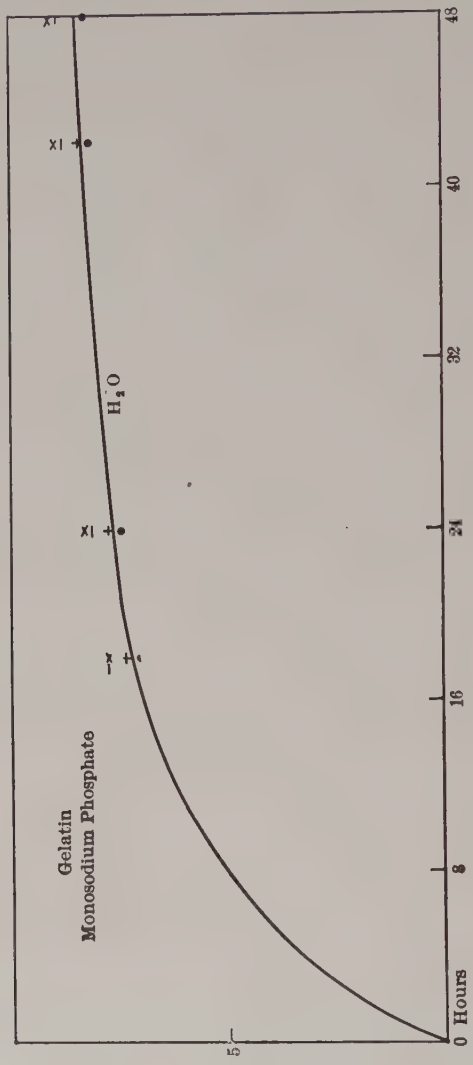


FIGURE 168.

body, and citric because of its great rôle in the plant economy. From the standardized solutions of these acids and of sodium hydroxid were then made the necessary primary, binary or ternary

salts, by mixing the acid and alkali together in the theoretically necessary amounts.

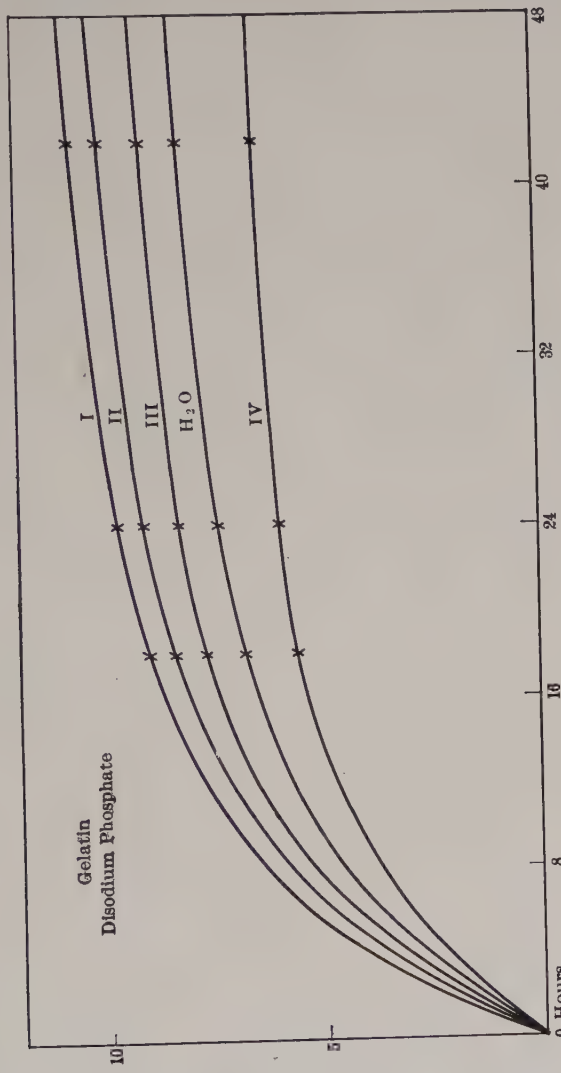


FIGURE 169.

The figures and tables are largely self-explanatory. The changes in weight (water absorption) of the gelatin discs at the end of different periods are calculated in terms of the original dry weight of the disc taken as unity.

§ 1

It was necessary, first, to determine the amounts of water absorbed by gelatin in different concentration of *the mono-, di-,*

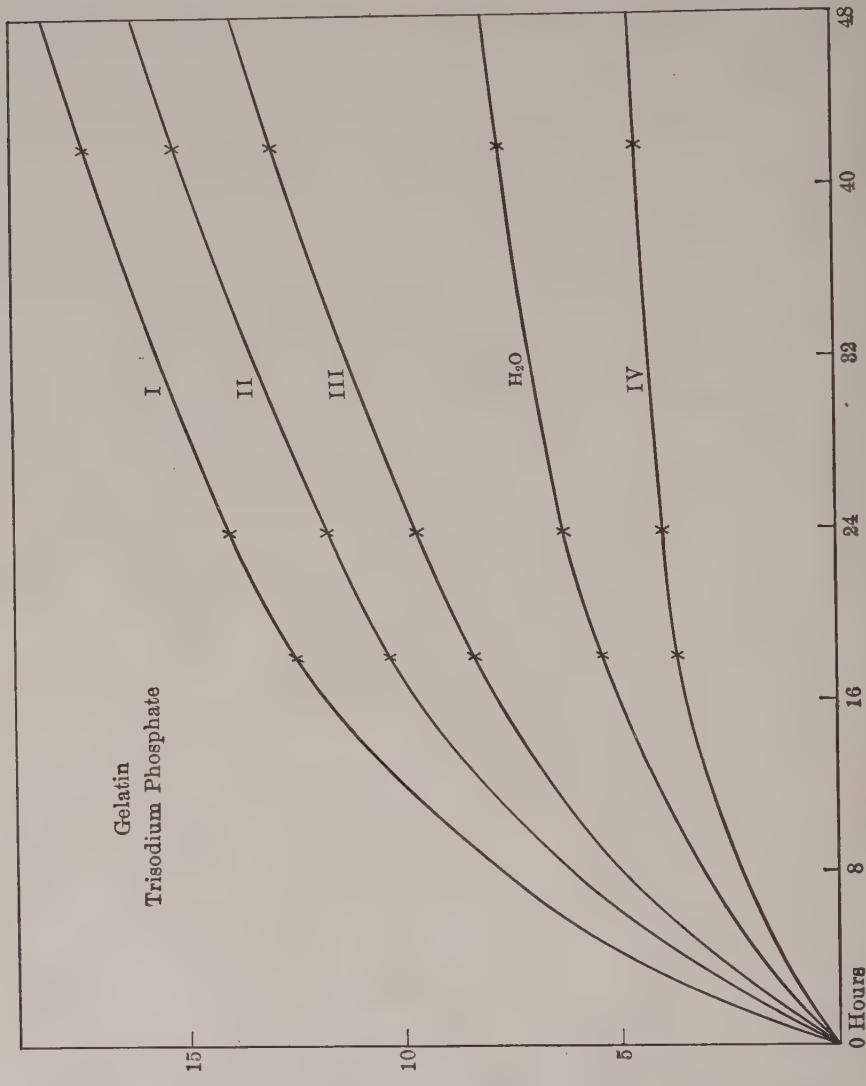


FIGURE 170.

and trisodium phosphates and to discover how long a time is necessary before this water absorption is approximately complete.

The results of three such experiments are shown in the curves of Figs. 168, 169 and 170, as well as in Tables CV, CVI and CVII, which contain the data from which the curves are drawn.

TABLE CV

GELATIN—*Monosodium phosphate*

Dry weight of gelatin disc.	0.311	0.312	0.312	0.314	0.310
Solution	5 cc. m/1 NaH_2PO_4 +95 cc. H_2O	15 cc. m/1 NaH_2PO_4 +85 cc. H_2O	25 cc. m/1 NaH_2PO_4 +75 cc. H_2O	50 cc. m/1 NaH_2PO_4 +50 cc. H_2O	100 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.				
18	7.31	7.75	7.73	7.12	7.30
24	7.71	8.25	8.16	7.55	7.60
42	8.27	9.00	8.83	8.20	8.45
48	8.50	9.20	9.12	8.38	8.90
66	8.65	9.37	9.25	8.60	9.80
89	9.03	9.87	9.73	9.00	11.91
	I	II	III	IV	H_2O

TABLE CVI

GELATIN—*Disodium phosphate*

Dry weight of gelatin disc.	0.317	0.317	0.319	0.319	0.315
Solution	5 cc. m/1 Na_2HPO_4 +95 cc. H_2O	15 cc. m/1 Na_2HPO_4 +85 cc. H_2O	25 cc. m/1 Na_2HPO_4 +75 cc. H_2O	50 cc. m/1 Na_2HPO_4 +50 cc. H_2O	100 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.				
18	9.10	8.57	7.80	5.60	6.84
24	9.74	9.16	8.30	5.91	7.41
42	10.65	10.08	9.06	6.40	8.20
48	10.91	10.32	9.30	6.56	8.60
66	11.16	10.70	9.63	6.74	10.43
89	11.65	11.22	10.20	7.24	11.22
	I	II	III	IV	H_2O

As evidenced in Fig. 168, gelatin swells little more or little less in any solution of monosodium phosphate between the concentrations of m/20 and m/2 than it does in pure water. Fig. 169 shows that disodium phosphate in its lower concentrations tends to increase the swelling of gelatin. A maximal swelling is observed

TABLE CVII

GELATIN—*Trisodium phosphate*

Dry weight of gelatin disc.	0.321	0.322	0.322	0.323	0.320
Solution	5 cc. m/1 Na_3PO_4 +95 cc. H_2O	15 cc. m/1 Na_3PO_4 +85 cc. H_2O	25 cc. m/1 Na_3PO_4 +75 cc. H_2O	50 cc. m/1 Na_3PO_4 +50 cc. H_2O	100 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.				
18	12.44	10.30	8.44	3.77	5.32
24	13.97	11.67	9.62	4.06	6.52
42	17.31	15.28	12.94	4.63	7.75
48	18.26	16.61	14.10	4.83	8.20
66	20.93	19.71	17.20	5.10	9.21
89	22.46	22.22	21.80	5.55	10.72
	I	II	III	IV	H_2O

in the *least* concentrated solution of this salt. With increasing concentration the amount of swelling decreases so that by the time the m/2 disodium phosphate solution is reached, the swelling of the gelatin is distinctly less than in pure water. A similar rule holds for like concentrations of trisodium phosphate, as shown in Fig. 170. Gelatin swells distinctly more in low concentrations of trisodium phosphate than in water, though reverse conditions come to obtain when the concentration of the phosphate is sufficiently increased.

The curves of Fig. 168, 169 and 170 suffice to show that gelatin practically attains its ultimate degree of swelling in a phosphate solution at the end of 24 to 48 hours. We therefore settled upon such approximate periods for the next series of experiments in which we sought to discover the amount of swelling shown by gelatin when immersed in solutions varying from pure phosphoric acid, on the one hand, through mono-, di- and trisodium phosphate mixtures to pure sodium hydroxid on the other. It was our purpose in this series to see how the amount of swelling fared as more and more of the initially pure phosphoric acid was replaced by the mono-, di- or trisodium salt. The result is shown in Table CVIII and Fig. 171. The curves show the amounts of swelling at the end of 18 and 24 hours. The low point in the curve indicative of least swelling is representative of the effects observed in the phosphate mixture numbered 6 in Table CVIII. As readily

TABLE CVIII

GELATIN—*Phosphoric acid to phosphates, to sodium hydroxid*

Dry weight of gelatin disc.	0.363	0.367	0.367	0.368	0.368	0.368	0.368
Solution	10 cc. n/1 H_3PO_4 +90 cc. H_2O	8 cc. n/1 H_3PO_4 +2 cc. m/1 NaH_2PO_4 +90 cc. H_2O	6 cc. n/1 H_3PO_4 +4 cc. m/1 NaH_2PO_4 +90 cc. H_2O	4 cc. n/1 H_3PO_4 +6 cc. m/1 NaH_2PO_4 +90 cc. H_2O	2 cc. n/1 H_3PO_4 +8 cc. m/1 NaH_2PO_4 +90 cc. H_2O	10 cc. m/1 NaH_2PO_4 +90 cc. H_2O	8 cc. m/1 NaH_2PO_4 +2 cc. m/1 Na_2HPO_4 +90 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.						
18	36.51	29.14	25.60	20.21	16.24	7.42	8.21
24	44.55 (1)	35.16 (2)	29.70 (3)	24.23 (4)	19.86 (5)	8.28 (6)	9.31 (7)

Dry weight of gelatin disc.	0.369	0.371	0.371	0.377	0.382	0.383	0.383
Solution	6 cc. m/1 NaH_2PO_4 +4 cc. m/1 Na_2HPO_4 + 90 cc. H_2O	4 cc. m/1 NaH_2PO_4 +6 cc. m/1 Na_2HPO_4 +90 cc. H_2O	2 cc. m/1 NaH_2PO_4 +8 cc. m/1 Na_2HPO_4 +90 cc. H_2O	10 cc.m/1 Na_2HPO_4 +90 cc. m/1 H_2O	8 cc. m/1 Na_2HPO_4 +2 cc. m/1 Na_3PO_4 +90 cc. H_2O	6 cc. m/1 Na_2HPO_4 +4 cc. m/1 Na_3PO_4 +90 cc. H_2O	4 cc. m/1 Na_2HPO_4 +6 cc. m/1 Na_3PO_4 +90 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.						
18	8.44	8.50	8.90	8.61	9.52	10.86	10.51
24	9.49 (8)	9.56 (9)	10.05 (10)	9.85 (11)	11.04 (12)	13.09 (13)	12.63 (14)

Dry weight of gelatin disc.	0.383	0.384	0.385	0.389	0.391	0.393	0.384
Solution	2 cc. m/1 Na_2HPO_4 +8 cc. m/1 Na_3PO_4 +90 cc. H_2O	10 cc. m/1 Na_3PO_4 +90 cc. H_2O	8 cc. m/1 Na_3PO_4 +2 cc. n/1 NaOH +90 cc. H_2O	6 cc. m/1 Na_3PO_4 +4 cc. n/1 NaOH +90 cc. H_2O	4 cc. m/1 Na_3PO_4 +6 cc. n/1 NaOH +90 cc. H_2O	2 cc. m/1 Na_3PO_4 +8 cc. n/1 NaOH +90 cc. H_2O	100 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.						
18	10.55	12.60	14.51	17.27	20.22	dissolving	6.86
24	12.81 (15)	17.45 (16)	21.45 (17)	dissolved (18)	dissolved (19)	dissolving (20)	7.77 (H_2O)

apparent, every increase in acid content to the left of this point is followed by increased swelling and the same is true for every increase in alkali content to the right of this point.

It is an interesting fact that the hydrogen ion concentration of Solution 6 is about that indicated by the turning point of methyl red ($10^{-6}C_H$). While we would not have it thought that the behavior of gelatin is at once to be paralleled with that of our body proteins, it is a fact that clinical observation indicates that urinary hydrogen ion acidities approach an unsafe height when they begin to lie persistently above this point.[1]

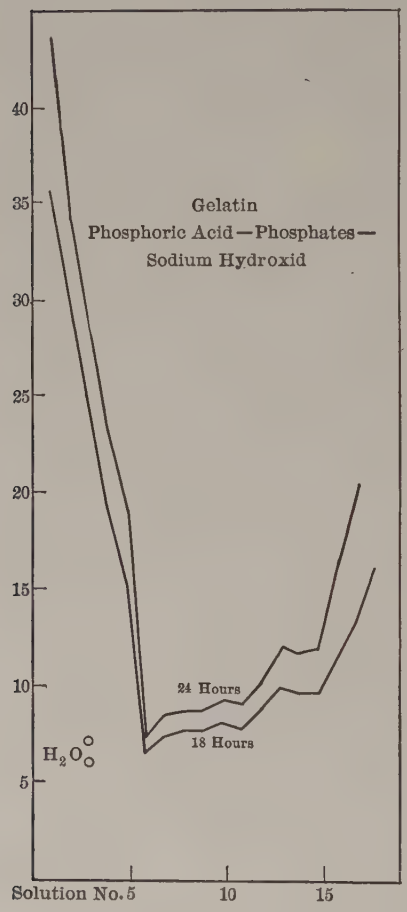


FIGURE 171.

Since the concentration of the phosphate mixtures employed in the experiments just described is relatively high (m/10), we did a second series at a concentration approximately that of the phosphates in the human body. The results are shown in Fig. 172 and Table CIX. The general shapes of the two curves which again represent the amounts of swelling attained in the different solutions at the ends of 18 and 42 hours are identical with those shown in Fig. 171. It is of interest to point out that the low point in the swelling curves representative of the effects of this more dilute phosphate mixture falls *below* the amount of swelling attained in pure

[1] MARTIN H. FISCHER: Trans. Assoc. Am. Phys., 27, 630 (1912); also page 773.

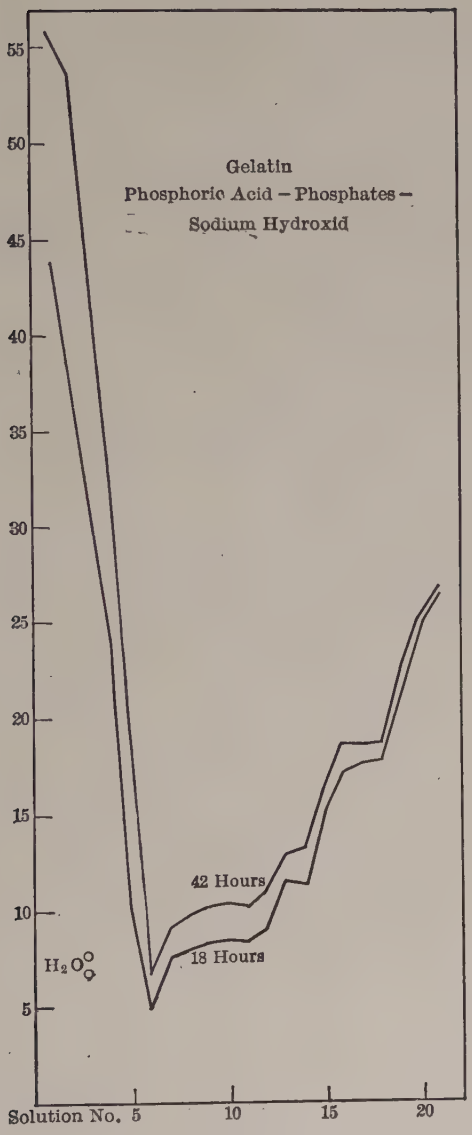


FIGURE 172.

water. There is, however, a relatively greater swelling as we move from this minimal point either in the direction of an increased acid or increased alkali content of the solutions, even

TABLE CIX

GELATIN—*Phosphoric acid to phosphates, to sodium hydroxid*

Dry weight of gelatin disc.	0.401	0.402	0.403	0.404	0.406	0.409	0.409
Solution	1 cc. n/1 H_3PO_4 +99 cc. H_2O	0.8 cc. n/1 H_3PO_4 +0.2 cc. m/1 NaH_2PO_4 +99 cc. H_2O	0.6 cc. n/1 H_3PO_4 +0.4 cc. m/1 NaH_2PO_4 +99 cc. H_2O	0.4 cc. n/1 H_3PO_4 +0.6 cc. m/1 NaH_2PO_4 +99 cc. H_2O	0.2 cc. n/1 H_3PO_4 +0.8 cc. m/1 NaH_2PO_4 +99 cc. H_2O	1 cc. m/1 NaH_2PO_4 +99 cc. H_2O	0.8 cc. m/1 NaH_2PO_4 +0.2 cc. m/1 Na_2HPO_4 +99 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.						
18	44.00	37.60	31.02	22.94	10.49	5.15	7.65
42	55.97 (1)	53.97 (2)	42.84 (3)	32.73 (4)	17.54 (5)	6.88 (6)	9.14 (7)

Dry weight of gelatin disc.	0.409	0.409	0.411	0.414	0.414	0.414	0.417
Solution	0.6 cc. m/1 NaH_2PO_4 +0.4 cc. m/1 Na_2HPO_4 +99 cc. H_2O	0.4 cc. m/1 NaH_2PO_4 +0.6 cc. m/1 Na_2HPO_4 +99 cc. H_2O	0.2 cc. m/1 NaH_2PO_4 +0.8 cc. m/1 Na_2HPO_4 +99 cc. H_2O	1 cc. m/1 Na_2HPO_4 +99 cc. H_2O	0.8 cc. m/1 Na_2HPO_4 +0.2 cc. m/1 Na_3PO_4 +99 cc. H_2O	0.6 cc. m/1 Na_2HPO_4 +0.4 cc. m/1 Na_3PO_4 +99 cc. H_2O	0.4 cc. m/1 Na_2HPO_4 +0.6 cc. m/1 Na_3PO_4 +99 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.						
18	8.00	8.42	8.55	8.48	9.20	11.64	11.42
42	9.80 (8)	10.24 (9)	10.50 (10)	10.31 (11)	10.98 (12)	12.90 (13)	13.26 (14)

Dry weight of gelatin disc.	0.419	0.420	0.421	0.424	0.425	0.425	0.426	0.408
Solution	0.2 cc. m/1 Na_2HPO_4 +0.8 cc. m/1 Na_3PO_4 +99 cc. H_2O	1 cc. m/1 Na_3PO_4 +99 cc. H_2O	0.8 cc. m/1 Na_3PO_4 +0.2 cc. n/1 NaOH +99 cc. H_2O	0.6 cc. m/1 Na_3PO_4 +0.4 cc. n/1 NaOH +99 cc. H_2O	0.4 cc. m/1 Na_3PO_4 +0.6 cc. n/1 NaOH +99 cc. H_2O	0.2 cc. m/1 Na_3PO_4 +0.8 cc. n/1 NaOH +99 cc. H_2O	1 cc. n/1 NaOH +99 cc. H_2O	100 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.							
18	15.20	17.37	17.72	17.88	21.57	25.08	26.65	6.09
42	16.44 (15)	18.77 (16)	18.74 (17)	18.84 (18)	21.74 (19)	25.43 (20)	27.06 (21)	7.50 (H_2O)

though the proportions in the various mixtures are identical with those used in the experiments of Table CVIII. The absolute

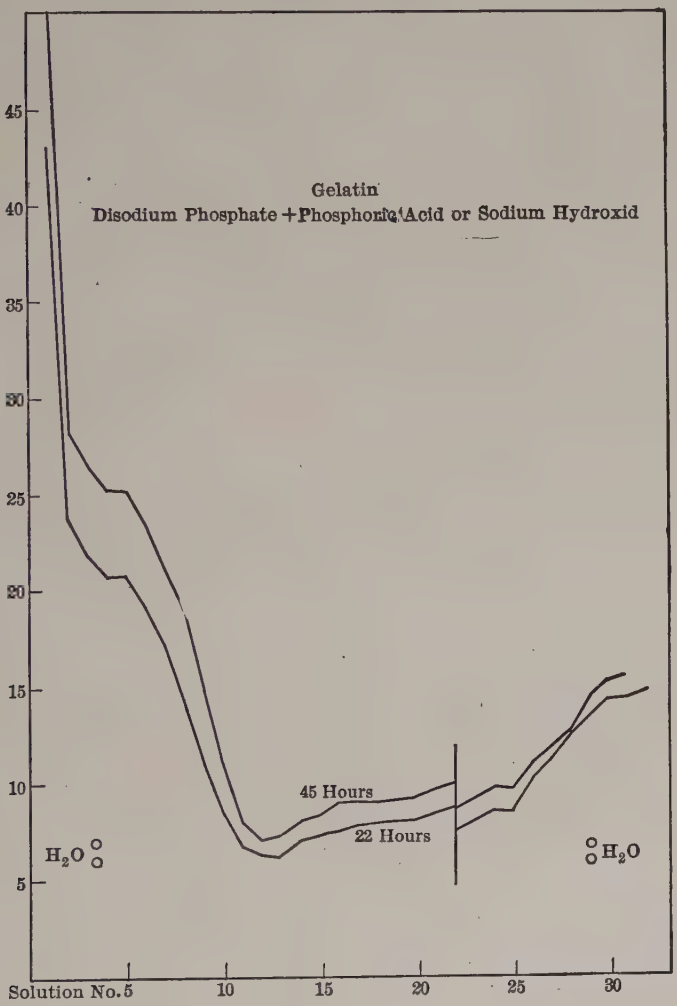


FIGURE 173.

amounts of swelling in the acid and alkaline extremes of these more dilute phosphate mixtures are distinctly higher than in the more concentrated phosphate series previously described.

In the experiments listed in Tables CVIII and CIX, the molar

concentration of the phosphate is the same throughout. While the curves of Figs. 171 and 172 show that every increase in the acid or alkali content of the phosphate mixture on either side of a low point is followed by an increased water absorption on the part of the immersed protein, it might be argued that such conditions do not obtain in the living organism where, it might be insisted, we begin with a definite concentration of a certain phosphate and then see an acid or an alkali added to this. That under such circumstances we also get a progressive increase in swelling as either

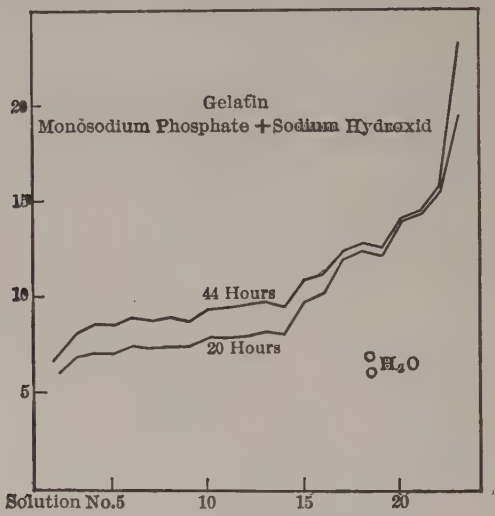


FIGURE 174.

the acid or alkali content of the mixture rises is shown in Figs. 173 and 174 and Tables CX and CXI. The first of these figures and tables begins with a fixed concentration of disodium phosphate (m/100), the second, with the same concentration of the monosodium salt.

A set of experiments was next made by beginning with a fixed concentration of acid (3/100 n) and adding to this progressively greater amounts of alkali. Under such circumstances there are seen, of course, the double effects of decrease in concentration of free acid with increase in amount of phosphate present. The general shape of the water absorption curve as shown in Fig. 175 and Table CXII is, however, that familiar to us from the previous

TABLE CX

GELATIN—*Disodium phosphate+phosphoric acid or sodium hydroxid*

Dry wt. of gelatin disc.	0.443	0.441	0.438	0.437	0.436	0.434	0.434
Solution	100 cc. H_2O	2 cc. n/1 H_3PO_4 +98 cc. H_2O	4 cc. m/4 Na_2HPO_4 +2.0 cc. n/1 H_3PO_4 +94 cc. H_2O	4 cc. m/4 Na_2HPO_4 +1.9 c.c. n/1 H_3PO_4 +94.1 cc. H_2O	4 cc. m/4 Na_2HPO_4 +1.8 cc. n/1 H_3PO_4 +94.2 cc. H_2O	4 cc. m/4 Na_2HPO_4 +1.7 cc. n/1 H_3PO_4 +94.3 cc. H_2O	4 cc. m/4 Na_2HPO_4 +1.6 cc. n/1 H_3PO_4 +94.4 c.c H_2O_4
Hrs. in the solution.	Gain in parts of one part of gelatin.						
22	6.28	43.00	23.70	21.70	20.73	20.80	19.14
45	7.20 (H_2O)	50.40 (1)	28.34 (2)	26.50 (3)	25.36 (4)	25.25 (5)	23.47 (6)

Dry wt. of gelatin disc.	0.434	0.433	0.433	0.431	0.431	0.423	0.422
Solution	4 cc. m/4 Na_2HPO_4 +1.5 cc. n/1 H_3PO_4 +94.5 cc. H_2O	4 cc. m/4 Na_2HPO_4 +1.4 cc. n/1 H_3PO_4 +94.6 cc. H_2O	4 cc. m/4 Na_2HPO_4 +1.3 cc. n/1 H_3PO_4 +94.7 cc. H_2O	4 cc. m/4 Na_2HPO_4 +1.2 cc. n/1 H_3PO_4 +94.8 cc. H_2O	4 cc. m/4 Na_2HPO_4 +1.1 cc. n/1 H_3PO_4 +94.9 cc. H_2O	4 cc. m/4 Na_2HPO_4 +1.0 cc. n/1 H_3PO_4 +95 cc. H_2O	4 cc. m/4 Na_2HPO_4 +0.9 cc. n/1 H_3PO_4 +95.1 cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.						
22	17.11	14.23	11.00	8.47	6.70	6.28	6.22
45	21.17 (7)	19.00 (8)	15.00 (9)	11.10 (10)	8.00 (11)	7.10 (12)	7.37 (13)

Dry wt. of gelatin disc.	0.421	0.420	0.419	0.419	0.416	0.415	0.414
Solution	4 cc. m/4 Na_2HPO_4 +0.8 cc. n/1 H_3PO_4 +95.2 cc. H_2O	4 cc. m/4 Na_2HPO_4 +0.7 cc. n/1 H_3PO_4 +95.3 cc. H_2O	4 cc. m/4 Na_2HPO_4 +0.6 cc. n/1 H_3PO_4 +95.4 cc. H_2O	4 cc. m/4 Na_2HPO_4 +0.5 cc. n/1 H_3PO_4 +95.5 cc. H_2O	4 cc. m/4 Na_2HPO_4 +0.4 cc. n/1 H_3PO_4 +95.6 cc. H_2O	4 cc. m/4 Na_2HPO_4 +0.3 cc. n/1 H_3PO_4 +95.7 cc. H_2O	4 cc. m/4 Na_2HPO_4 + 0.2 cc. n/1 H_3PO_4 +95.8 cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.						
22	7.00	7.33	7.50	7.80	7.90	8.00	8.16
45	8.03 (14)	8.34 (15)	9.14 (16)	9.07 (17)	9.08 (18)	9.10 (19)	9.30 (20)

TABLE CX—*Concluded*

Dry wt. of gelatin disc.	0.413	0.413	0.405	0.406	0.406	0.407	0.407
Solution	4 cc. m/4 Na_2HPO_4 +0.1 cc. n/1 H_3PO_4 +95.9 cc. H_2O	4 cc. m/4 Na_2HPO_4 +96 cc. H_2O	4 cc. m/4 Na_2HPO_4 +96 cc. H_2O	4 cc. m/4 Na_2HPO_4 +0.1 cc. n/1 NaOH +95.9 cc. H_2O	4 cc. m/4 Na_2HPO_4 +0.2 cc. n/1 NaOH +95.8 cc. H_2O	4 cc. m/4 Na_2HPO_4 +0.3 cc. n/1 NaOH +95.7 cc. H_2O	4 cc. m/4 Na_2HPO_4 +0.4 cc. n/1 NaOH +95.6 cc. H_2O
Hrs. in the solution.	Gain in parts of one part in gelatin.						
22	8.45	8.68	7.63	8.03	8.57	8.60	10.29
45	9.70 (21)	10.06 (22)	8.72 (23)	9.20 (24)	9.82 (25)	9.70 (26)	11.05 (27)

Dry wt. of gelatin disc.	0.407	0.408	0.408	0.409	0.410	0.411	0.412
Solution	4 cc. m/4 Na_2HPO_4 +0.5 cc. n/1 NaOH +95.5 cc. H_2O	4 cc. m/4 Na_2HPO_4 +0.6 cc. n/1 NaOH +95.4 cc. H_2O	4 cc. m/4 Na_2HPO +0.7 cc. n/1 NaOH +95.3 cc. H_2O	4 cc. m/4 Na_2HPO_4 +0.8 cc. n/1 NaOH +95.2 cc. H_2O	4 cc. m/4 Na_2HPO_4 +0.9 cc. n/1 NaOH +95.1 cc. H_2O	4 cc. m/4 Na_2HPO_4 +1.0 cc. n/1 NaOH +95 cc. H_2O	100 cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.						
22	11.21	12.65	13.41	14.40	14.57	14.87	6.04
45	11.80 (28)	12.72 (29)	13.65 (30)	15.40 (31)	15.70 (32)	14.81 (33)	6.82 (H_2O)

experiments. A low point is again found in the middle of the curve when one-third of the replaceable hydrogen of the phosphoric acid has been neutralized by alkali, in other words, when we deal with a solution which is practically pure monosodium phosphate. Addition of more alkali leads to increased swelling up to the high point at the right of the curve which represents the theoretically pure solution of trisodium phosphate.

A final series of phosphate experiments is shown in Fig. 176 and Table CXIII. Here a fixed amount of alkali (3/100 n) was neutralized by adding gradually increasing amounts of phosphoric acid. There are shown, in other words, the effects of simultaneous reduction of alkali with increase in amount of phosphate present.

TABLE CXI

GELATIN—*Monosodium phosphate, with increasing amounts of sodium hydroxid*

Dry wt. of gelatin disc.	0.388	0.390	0.391	0.392	0.392	0.393	0.393	0.393
Solution	1 cc. m/1 NaH_2PO_4 +99 cc. H_2O	1 cc. m/1 NaH_2PO_4 +0.1 cc. n/1 NaOH +98.9 cc. H_2O	1 cc. m/1 NaH_2PO_4 +0.2 cc. n/1 NaOH +98.8 cc. H_2O	1 cc. m/1 NaH_2PO_4 +0.3 cc. n/1 NaOH +98.7 cc. H_2O	1 cc. m/1 NaH_2PO_4 +0.4 cc. n/1 NaOH +98.6 cc. H_2O	1 cc. m/1 NaH_2PO_4 +0.5 cc. n/1 NaOH +98.5 cc. H_2O	1 cc. m/1 NaH_2PO_4 +0.6 cc. n/1 NaOH +98.4 cc. H_2O	1 cc. m/1 NaH_2PO_4 +0.7 cc. n/1 NaOH +98.3 cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.							
20	5.90	6.90	7.11	7.11	7.65	7.47	7.50	7.53
44	6.78	8.10	8.44	8.56	9.00	8.80	9.00	8.83
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)

Dry wt. of gelatin disc.	0.394	0.395	0.395	0.397	0.398	0.400	0.400
Solution	1 cc. m/1 NaH_2PO_4 +0.8 cc. n/1 NaOH +98.2 cc. H_2O	1 cc. m/1 NaH_2PO_4 +0.9 cc. n/1 NaOH +98.1 cc. H_2O	1 cc. m/1 NaH_2PO_4 +1.0 cc. n/1 NaOH +98 cc. H_2O	1 cc. m/1 NaH_2PO_4 +1.1 cc. n/1 NaOH +97.9 cc. H_2O	1 cc. m/1 NaH_2PO_4 +1.2 cc. n/1 NaOH +97.8 cc. H_2O	1 cc. m/1 NaH_2PO_4 +1.3 cc. n/1 NaOH +97.7 cc. H_2O	1 cc. m/1 NaH_2PO_4 +1.4 cc. n/ NaOH +97.6 cc. H_2O
Hrs. in the solution.	Gain in parts in one part of gelatin						
20	8.02	8.12	8.17	8.37	8.20	9.80	10.24
44	9.45	9.57	9.70	9.84	9.60	11.03	11.30
	(9)	(10)	(11)	(12)	(13)	(14)	(15)

Dry wt. of gelatin disc.	0.401	0.403	0.403	0.403	0.404	0.405	0.405	0.405
Solution	1 cc. m/1 NaH_2PO_4 +1.5 cc. n/1 NaOH +97.5 cc. H_2O	1 cc. m/1 NaH_2PO_4 +1.6 cc. n/1 NaOH +97.4 cc. H_2O	1 cc. m/1 NaH_2PO_4 +1.7 cc. n/1 NaOH +97.3 cc. H_2O	1 cc. m/1 NaH_2PO_4 +1.8 cc. n/1 NaOH +97.2 cc. H_2O	1 cc. m/1 NaH_2PO_4 +1.9 cc. n/1 NaOH +97.1 cc. H_2O	1 cc. m/1 NaH_2PO_4 +2.0 cc. n/1 NaOH +97 cc. H_2O	2.0 cc. n/1 NaOH +98 cc. H_2O	100 cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.							
20	12.00	12.51	12.28	14.04	14.42	15.55	19.65	6.13
44	12.54	12.94	12.56	14.10	14.47	15.42	23.91	7.06
	(16)	(17)	(18)	(19)	(20)	(21)	(22)	(H_2O)

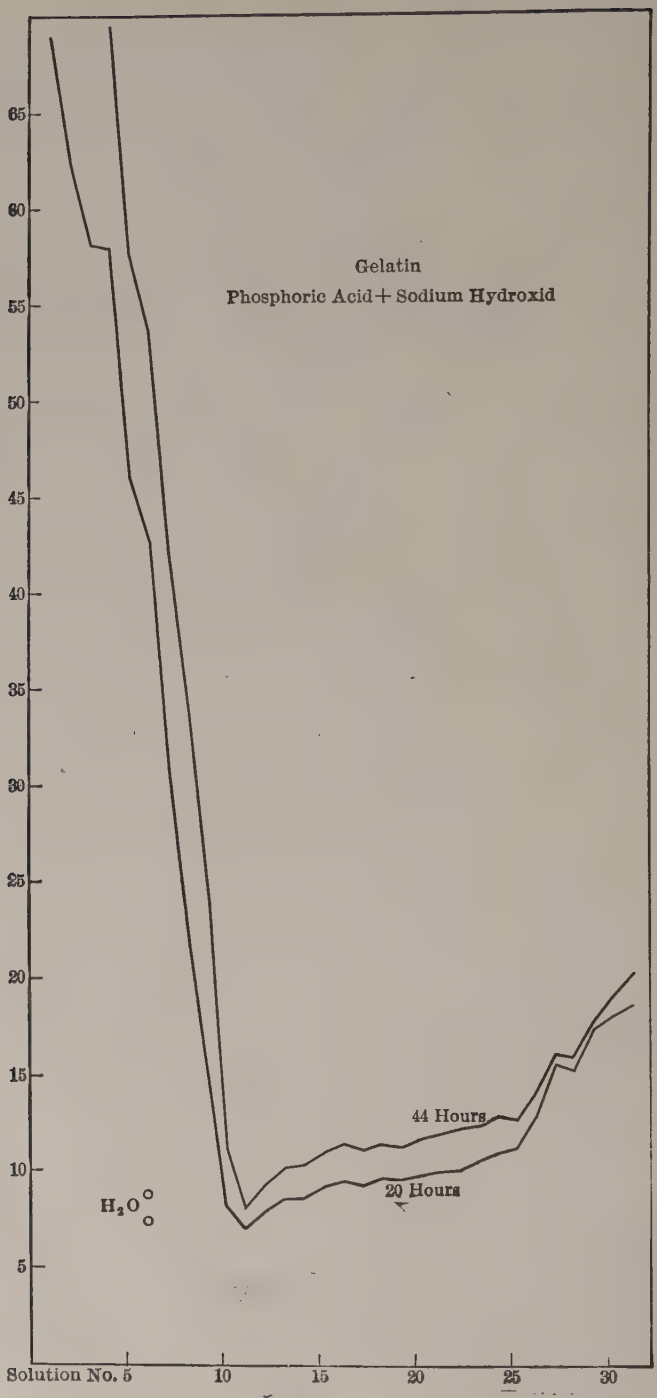

Gelatin
Phosphoric Acid + Sodium Hydroxid
44 Hours
20 Hours
H_2O
65
60
55
50
45
40
35
30
25
20
15
10
5
Solution No. 5
10
15
20
25
30

FIGURE 175.

TABLE CXII

GELATIN—*Phosphoric acid with increasing amounts of sodium hydroxid*

Dry wt. of gelatin disc.	0.343	0.343	0.345	0.347	0.360	0.363	0.365	0.367
Solution	3 cc. n/1 H_3PO_4 +97 cc. H_2O	3 cc. n/1 H_3PO_4 +0.1 cc. n/1 NaOH +96.9cc. H_2O	3 cc. n/1 H_3PO_4 +0.2 cc. n/1 NaOH +96.8cc. H_2O	3 cc. n/1 H_3PO_4 +0.3 cc. n/1 NaOH +96.7cc. H_2O	3 cc. n/1 H_3PO_4 +0.4 cc. n/1 NaOH +96.6cc. H_2O	3 cc. n/1 H_3PO_4 +0.5 cc. n/1 NaOH +96.5cc. H_2O	3 cc. n/1 H_3PO_4 +0.6 cc. n/1 NaOH +96.4cc. H_2O	3 cc. n/1 H_3PO_4 +0.7 cc. n/1 NaOH +96.3cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.							
20	69.32	62.85	58.65	58.45	46.60	43.00	31.00	22.31
44	84.68	75.11	70.60	69.90	58.17	54.16	42.20	33.87
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)

Dry wt. of gelatin disc.	0.367	0.367	0.367	0.370	0.370	0.370	0.371	0.374
Solution	3 cc. n/1 H_3PO_4 +0.8 cc. n/1 NaOH +96.2cc. H_2O	3 cc. n/1 H_3PO_4 +0.9 cc. n/1 NaOH +96.1cc. H_2O	3 cc. n/1 H_3PO_4 +1.0 cc. n/1 NaOH +96.0cc. H_2O	3 cc. n/1 H_3PO_4 +1.1 cc. n/1 NaOH +95.9cc. H_2O	3 cc. n/1 H_3PO_4 +1.2 cc. n/1 NaOH +95.8cc. H_2O	3 cc. n/1 H_3PO_4 +1.3 cc. n/1 NaOH +95.7cc. H_2O	3 cc. n/1 H_3PO_4 +1.4 cc. n/1 NaOH +95.6cc. H_2O	3 cc. n/1 H_3PO_4 +1.5 cc. n/1 NaOH +95.5cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.							
20	15.30	8.31	7.10	8.03	8.68	8.74	9.35	9.60
44	24.32	11.28	8.27	9.41	10.27	10.44	11.16	11.56
	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)

Dry wt. of gelatin disc.	0.380	0.382	0.383	0.384	0.386	0.385	0.388	0.388
Solution	3 cc. n/1 H_3PO_4 +1.6 cc. n/1 NaOH +95.4cc. H_2O	3 cc. n/1 H_3PO_4 +1.7 cc. n/1 NaOH +95.3cc. H_2O	3 cc. n/1 H_3PO_4 +1.8 cc. n/1 NaOH +95.2cc. H_2O	3 cc. n/1 H_3PO_4 +1.9 cc. n/1 NaOH +95.1cc. H_2O	3 cc. n/1 H_3PO_4 +2.0 cc. n/1 NaOH +95.0cc. H_2O	3 cc. n/1 H_3PO_4 +2.1 cc. n/1 NaOH +94.9cc. H_2O	3 cc. n/1 H_3PO_4 +2.2 cc. n/1 NaOH +94.8cc. H_2O	3 cc. n/1 H_3PO_4 +2.3 cc. n/1 NaOH +94.7cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.							
20	9.49	9.81	9.81	10.00	10.23	10.26	10.80	11.28
44	11.31	11.60	11.57	11.90	12.14	12.40	12.61	13.12
	(17)	(18)	(19)	(20)	(21)	(22)	(23)	(24)

TABLE CXII—*Concluded*

Dry wt. of gelatin disc.	0.388	0.388	0.389	0.391	0.391	0.392	0.394	0.394
Solution	3 cc. n/1 H_3PO_4 +2.4 cc. n/1 NaOH +94.6cc. H_2O	3 cc. n/1 H_3PO_4 +2.5 cc. n/1 NaOH +94.5cc. H_2O	3 cc. n/1 H_3PO_4 +2.6 cc. n/1 NaOH +94.4cc. H_2O	3 cc. n/1 H_3PO_4 +2.7 cc. 1/n NaOH +94.3cc. H_2O	3 cc. n/1 H_3PO_4 +2.8 cc. n/1 NaOH +94.2cc. H_2O	3 cc. n/1 H_3PO_4 +2.9 cc. n/1 NaOH +94.1cc. H_2O	3 cc. n/1 H_3PO_4 +3.0 cc. n/1 NaOH +94 cc. H_2O	100 cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.							
20	11.52	13.14	15.81	15.57	17.71	19.40	19.91	7.45
44	13.00	14.24	16.25	16.17	18.03	19.37	20.50	8.80
	(25)	(26)	(27)	(28)	(29)	(30)	(31)	(H_2O)

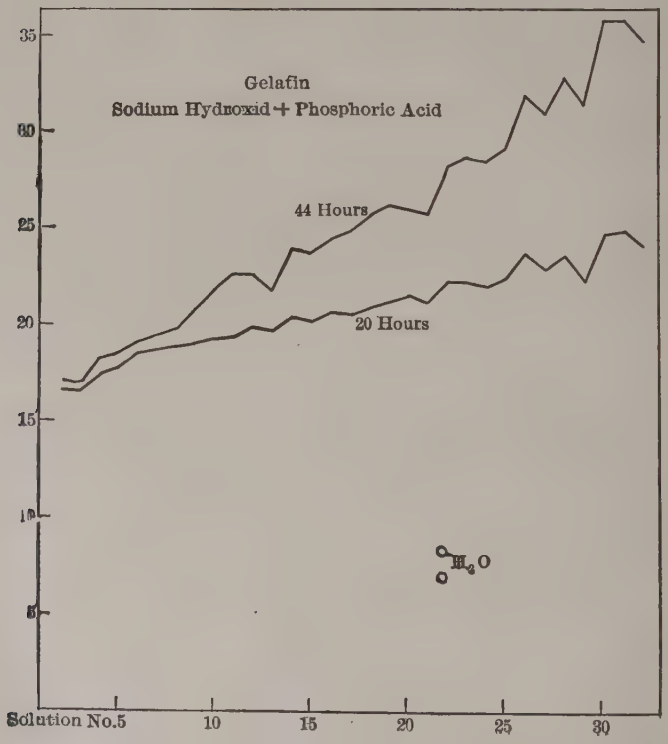


FIGURE 176.

TABLE CXIII

GELATIN—*Sodium hydroxid with decreasing amounts of phosphoric acid*

Dry wt. of gelatin disc.	0.347	0.346	0.343	0.342	0.341	0.341	0.340	0.340
Solution	3 cc. n/1 NaOH +3.0 cc. n/1 H_3PO_4 +94 cc. H_2O	3 cc. n/1 NaOH +2.9 cc. n/1 H_3PO_4 +94.1cc. H_2O	3 cc. n/1 NaOH +2.8 cc. n/1 H_3PO_4 +94.2cc. H_2O	3 cc. n/1 NaOH +2.7 cc. n/1 H_3PO_4 +94.3cc. H_2O	3 cc. n/1 NaOH +2.6 cc. n/1 H_3PO_4 +94.4cc. H_2O	3 cc. n/1 NaOH +2.5 cc. n/1 H_3PO_4 +94.5cc. H_2O	3 cc. n/1 NaOH +2.4 cc. n/1 H_3PO_4 +94.6cc. H_2O	3 cc. n/1 NaOH +2.3 cc. n/1 H_3PO_4 +94.7cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.							
20	16.46	16.40	17.17	17.55	18.32	18.36	18.70	18.85
44	17.00	16.69	18.02	18.30	18.82	18.80	19.53	20.53
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)

Dry wt. of gelatin disc.	0.340	0.339	0.338	0.338	0.338	0.338	0.337	0.336
Solution	3 cc. n/1 NaOH +2.2 cc. n/1 H_3PO_4 +94.8cc. H_2O	3 cc. n/1 NaOH +2.1 cc. n/1 H_3PO_4 +94.9cc. H_2O	3 cc. n/1 NaOH +2.0 cc. n/1 H_3PO_4 +95 cc. H_2O	3 cc. n/1 NaOH +1.9 cc. n/1 H_3PO_4 +95.1cc. H_2O	3 cc. n/1 NaOH +1.8 cc. n/1 H_3PO_4 +95.2cc. H_2O	3 cc. n/1 NaOH +1.7 cc. n/1 H_3PO_4 +95.3cc. H_2O	3 cc. n/1 NaOH +1.6 cc. n/1 H_3PO_4 +95.4cc. H_2O	3 cc. n/1 NaOH +1.5 cc. n/1 H_3PO_4 +95.5cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.							
20	19.00	19.15	19.65	19.47	20.25	20.03	20.45	20.35
44	21.60	22.42	22.43	21.65	23.76	23.55	24.37	24.70
	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)

Dry wt. of gelatin disc.	0.336	0.336	0.335	0.335	0.334	0.332	0.331	0.331
Solution	3 cc. n/1 NaOH +1.4 cc. n/1 H_3PO_4 +95.6cc. H_2O	3 cc. n/1 NaOH +1.3 cc. n/1 H_3PO_4 +95.7cc. H_2O	3 cc. n/1 NaOH +1.2 cc. n/1 H_3PO_4 +95.8cc. H_2O	3 cc. n/1 NaOH +1.1 cc. n/1 H_3PO_4 +95.9cc. H_2O	3 cc. n/1 NaOH +1.0 cc. n/1 H_3PO_4 +96 cc. H_2O	3 cc. n/1 NaOH +0.9 cc. n/1 H_3PO_4 +96.1cc. H_2O	3 cc. n/1 NaOH +0.8 cc. n/1 H_3PO_4 +96.2cc. H_2O	3 cc. n/1 NaOH +0.7 cc. n/1 H_3PO_4 +96.3cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.							
20	20.77	21.05	21.30	20.97	22.06	22.04	21.85	22.21
44	25.55	26.00	25.85	25.58	28.14	28.50	28.31	29.03
	(17)	(18)	(19)	(20)	(21)	(22)	(23)	(24)

TABLE CXIII—*Concluded*

Dry wt. of gelatin disc.	0.330	0.330	0.330	0.329	0.329	0.328	0.327	0.347
Solution	3 cc. n/1 NaOH + 0.6 cc. n/1 H_3PO_4 + 96.4 cc. H_2O	3 cc. n/1 NaOH + 0.5 cc. n/1 H_3PO_4 + 96.5 cc. H_2O	3 cc. n/1 NaOH + 0.4 cc. n/1 H_3PO_4 + 96.6 cc. H_2O	3 cc. n/1 NaOH + 0.3 cc. n/1 H_3PO_4 + 96.7 cc. H_2O	3 cc. n/1 NaOH + 0.2 cc. n/1 H_3PO_4 + 96.8 cc. H_2O	3 cc. n/1 NaOH + 0.1 cc. n/1 H_3PO_4 + 96.9 cc. H_2O	3 cc. n/1 NaOH + 97 cc. H_2O	100 cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.							
20	23.56	22.70	23.48	22.13	24.51	24.73	24.00	6.94
44	31.80	30.81	32.66	31.26	35.68	35.61	34.64	8.33
	(25)	(26)	(27)	(28)	(29)	(30)	(31)	(H_2O)

The water absorption curve falls as the neutralization progresses, until a low point is attained in the theoretically pure solution of trisodium phosphate.

TABLE CXIV

GELATIN—*Monosodium citrate*

Dry weight of gelatin disc.	0.370	0.373	0.373	0.373	0.370
Solution	5 cc. m/1 monosodium citrate + 95 cc. H_2O	15 cc. m/1 monosodium citrate + 85 cc. H_2O	25 cc. m/1 monosodium citrate + 75 cc. H_2O	50 cc. m/1 monosodium citrate + 50 cc. H_2O	100 cc. H_2O
Hours in the solution.	Gain in parts of one part gelatin.				
18	7.17	6.74	6.20	6.23	5.52
24	7.91	7.47	7.11	7.12	5.94
41	8.69	8.16	8.27	8.01	6.35
48	8.92	8.44	8.59	8.40	6 52
66	9.30	8.81	9.08	9.00	6.84
71	9.35	8.85	9.12	9.11	6.90
91	9.51	8.88	9.41	9.28	7.27
	(I)	(II)	(III)	(IV)	(H_2O)

§ 2

We studied next the effects of *citric acid and the citrates* upon the swelling of gelatin. The citrate solutions were prepared by adding

TABLE CXV

GELATIN—*Disodium citrate*

Dry weight of gelatin disc.	0.365	0.367	0.369	0.369	0.365
Solution	5 cc. m/1 disodium citrate +95 cc. H_2O	15 cc. m/1 disodium citrate +85 cc. H_2O	25 cc. m/1 disodium citrate +75 cc. H_2O	50 cc. m/1 disodium citrate +50 cc. H_2O	100 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.				
18	6.39	6.38	5.11	5.12	5.47
24	6.88	6.92	6.44	5.78	5.92
41	7.34	7.41	7.26	6.24	6.31
48	7.77	7.58	7.49	6.48	6.49
66	7.70	7.83	7.74	6.74	6.89
71	7.76	7.84	7.71	6.77	6.96
91	7.82	7.95	7.89	7.86	7.37
	(I)	(II)	(III)	(IV)	(H_2O)

TABLE CXVI

GELATIN—*Trisodium citrate*

Dry weight of gelatin disc.	0.363	0.363	0.363	0.364	0.363
Solution	5 cc. m/1 trisodium citrate +95 cc. H_2O	15 cc. m/1 trisodium citrate +85 cc. H_2O	25 cc. m/1 trisodium citrate +75 cc. H_2O	50 cc. m/1 trisodium citrate +50 cc. H_2O	100 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.				
18	7.12	6.42	5.51	3.12	5.53
24	7.75	7.01	6.04	3.52	5.98
41	8.23	7.51	6.51	3.90	6.35
48	8.50	7.69	6.68	4.02	6.58
66	8.73	7.95	6.93	4.21	6.99
71	8.73	7.96	6.96	4.23	7.08
91	8.81	8.06	7.04	4.30	7.62
	(I)	(II)	(III)	(IV)	(H_2O)

to each other the theoretically necessary amounts of carefully standardized citric acid and sodium hydroxid solutions.

In Figs. 177, 178 and 179, which portray graphically the experimental findings contained in Tables CXIV, CXV and CXVI, are shown the effects, respectively, of mono-, di- and trisodium

citrate in different concentrations upon the swelling of gelatin. As evident in Fig. 177, monosodium citrate in all the concentrations

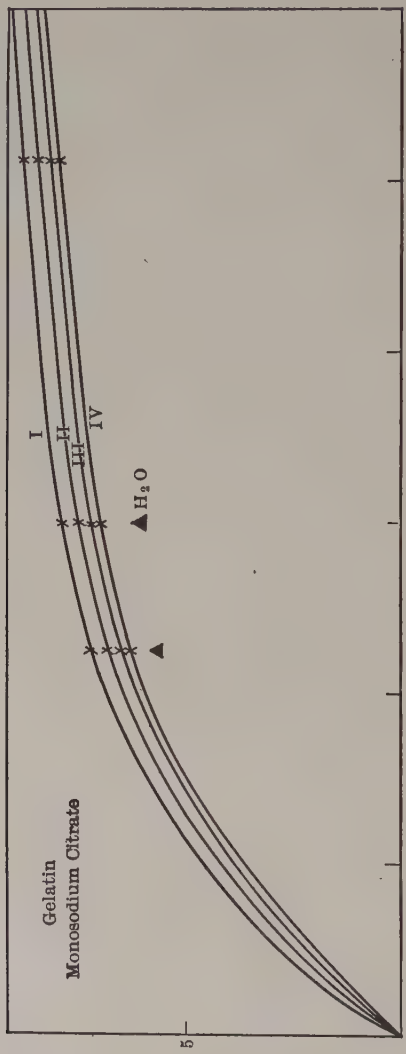


FIGURE 177.

used increases the amount of water absorbed by gelatin over and above the amount absorbed in pure water. The same is true of the lower concentrations of equimolar solutions of disodium

citrate. For both of these salts there is a progressive decrease in swelling with increase in the concentration of the salt. As evident

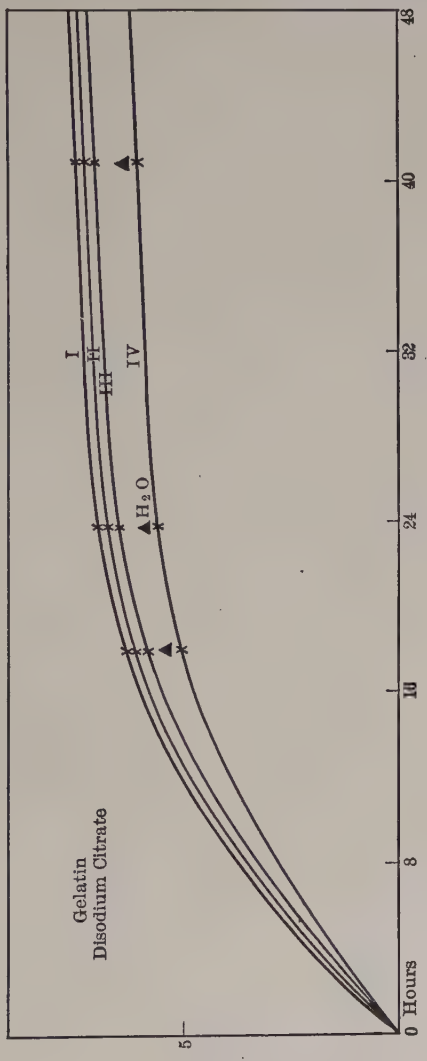


FIGURE 178.

in the lowermost curve of Fig. 178, a sufficiently high concentration of disodium citrate makes gelatin swell even less than in pure water. The effects of trisodium citrate are shown in Fig. 179.

Low concentrations of this salt also increase the amount of water absorption over the amount absorbed in pure water, but with

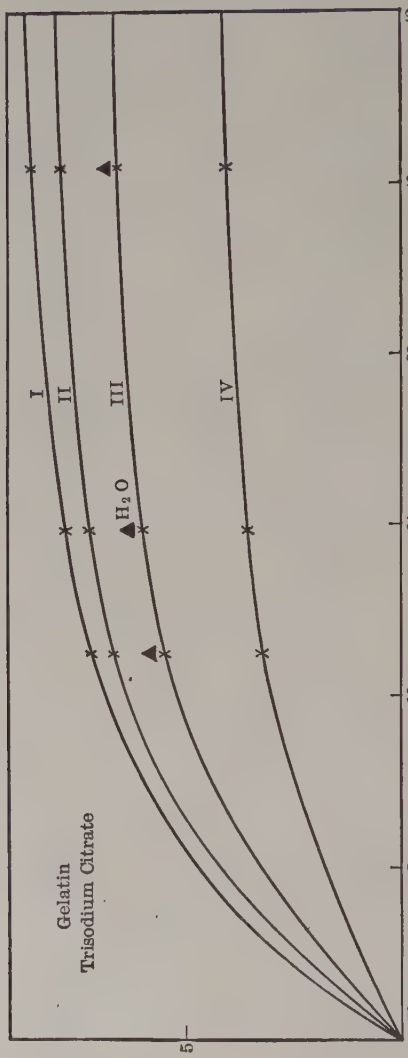


FIGURE 179.

increasing concentration there is less and less swelling, until the amounts of water absorbed in the higher concentrations of the trisodium citrate are distinctly less than in pure water.

Having determined in this fashion the effects of different concentrations of the different citrates, we investigated the swelling of gelatin in citrate mixtures varying from the extreme on the one side of pure citric acid through equimolar concentrations of mono-, di- and trisodium citrate to pure sodium hydroxid on the other. The results as shown in Fig. 180 and Table CXVII are self-explan-

TABLE CXVII

GELATIN—*Citric acid, through citrates, to sodium hydroxid*

Dry weight of gelatin disc.	0.332	0.334	0.335	0.335	0.336	0.338	0.339
Solution	10 cc. n/1 citric acid + 90 cc. H_2O	8 cc. n/1 citric acid + 2 cc. m/1 monosodium citrate + 90 cc. H_2O	6 cc. n/1 citric acid + 4 cc. m/1 monosodium citrate + 90 cc. H_2O	4 cc. n/1 citric acid + 6 cc. m/1 monosodium citrate + 90 cc. H_2O	2 cc. n/1 citric acid + 8 cc. m/1 monosodium citrate + 90 cc. H_2O	10 cc. m/1 monosodium citrate + 90 cc. H_2O	8 cc. m/1 monosodium citrate + 2 cc. m/1 disodium citrate + 90 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.						
24	46.10	27.58	18.29	14.11	11.08	9.02	7.66
48	51.08	33.14	22.71	17.04	13.09	10.40	8.84
72	60.70	36.72	25.10	18.53	14.18	11.16	9.47
	(1)	(2)	(3)	(4)	(5)	(6)	(7)

Dry weight of gelatin disc.	0.340	0.341	0.341	0.342	0.342	0.345	0.345
Solution	6 cc. m/1 monosodium citrate + 4 cc. m/1 disodium citrate + 90 cc. H_2O	4 cc. m/1 monosodium citrate + 6 cc. m/1 disodium citrate + 90 cc. H_2O	2 cc. m/1 monosodium citrate + 8 cc. m/1 disodium citrate + 90 cc. H_2O	10 cc. m/1 disodium citrate + 90 cc. H_2O	8 cc. m/1 disodium citrate + 2 cc. m/1 trisodium citrate + 90 cc. H_2O	6 cc. m/1 disodium citrate + 4 cc. m/1 trisodium citrate + 90 cc. H_2O	4 cc. m/1 disodium citrate + 6 cc. m/1 trisodium citrate + 90 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.						
24	7.60	7.50	7.55	8.02	8.05	8.22	8.26
48	8.61	8.45	8.44	8.93	8.96	8.80	9.23
72	9.27	9.00	9.08	9.46	9.50	9.48	10.02
	(8)	(9)	(10)	(11)	(12)	(13)	(14)

TABLE CXVII—*Concluded*

Dry wt. of gelatin disc.	0.346	0.350	0.351	0.352	0.352	0.353	0.353	0.350
Solution	2 cc. m/1 disodium citrate + 8 cc. m/1 trisodium citrate + 90 cc. H_2O	10 cc. m/1 trisodium citrate + 90 cc. H_2O	8 cc. m/1 trisodium citrate + 2 cc. n/1 NaOH + 90 cc. H_2O	6 cc. m/1 trisodium citrate + 4 cc. n/1 NaOH + 90 cc. H_2O	4 cc. m/1 trisodium citrate + 6 cc. n/1 NaOH + 90 cc. H_2O	2 cc. m/1 trisodium citrate + 8 cc. n/1 NaOH + 90 cc. H_2O	10 cc. n/1 NaOH + 90 cc. H_2O	100 cc. H_2O
Hrs. in the solution.	Gain in parts of one part of gelatin.							
24	8.19	8.16	10.51	14.22	17.01	24.22+	dis-solving	6.35
48	9.34	9.03	12.90	20.54	27.83+	dis-solving	dis-solved	7.12
72	9.54	9.41	15.06	28.83+	dis-solving			8.11
	(15)	(16)	(17)	(18)	(19)	(20)	(21)	H_2O

atory. The three curves show the amounts of water absorbed at the end of 24, 48 and 72 hours. As readily evident, most swelling occurs in the pure citric acid, and less and less swelling as the pure citric acid gives way to the monosodium citrate. Between monosodium citrate, disodium citrate and trisodium citrate there is little change in the amount of water absorbed, this portion of the curve describing a gentle arc. As the excess of alkali appears in the mixture, the curve again ascends steeply.

§ 3

The swelling of gelatin in carbonate mixtures has also been given some study. The results here again confirm the general conclusions previously cited for phosphates and citrates. In the carbonate series we began with pure sodium bicarbonate and gradually replaced this by molecularly equivalent amounts of sodium carbonate, and this in turn by sodium hydroxid. The effects upon the swelling of gelatin as we pass from the sodium bicarbonate through the sodium carbonate to sodium hydroxid is shown in Fig. 181 and Table CXVIII. The curves show the amounts of swelling at the end of $5\frac{1}{2}$, 29 and 53 hours. As is clearly apparent, gelatin swells more in a solution of sodium

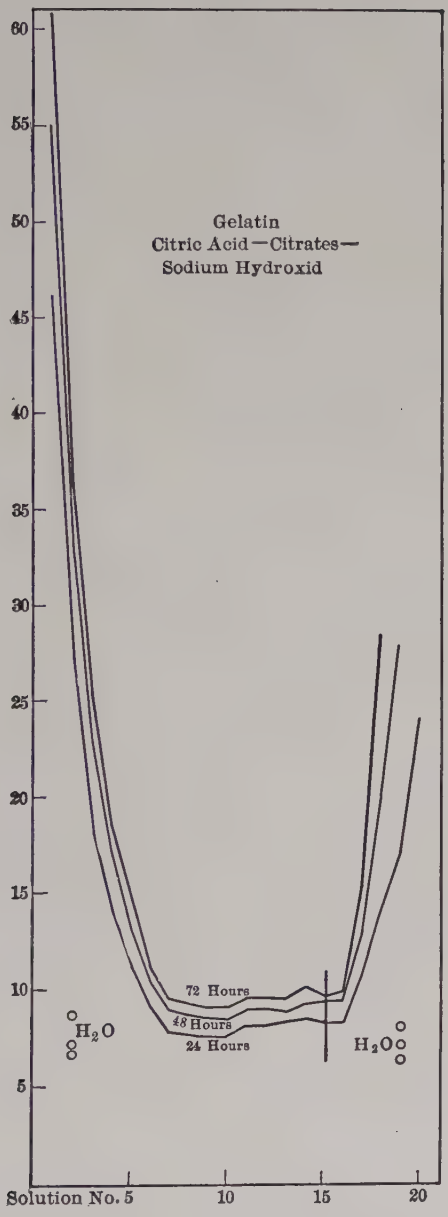

60
55
50
45
40
35
30
25
20
15
10
5
Gelatin
Citric Acid—Citrates—
Sodium Hydroxid
72 Hours
48 Hours
24 Hours
H_2O
H_2O
Solution No. 5
10
15
20

FIGURE 180.

TABLE CXVIII

GELATIN—*Sodium bicarbonate, to sodium carbonate, to sodium hydroxid*

Dry weight of gelatin disc.	0.368	0.369	0.370	0.370	0.371	0.371	0.372
Solution	2 cc. m/1 $NaHCO_3$ + 98 cc. H_2O	1.9 cc. m/1 $NaHCO_3$ + 0.1 cc. m/1 Na_2CO_3 + 98 cc. H_2O	1.8 cc. m/1 $NaHCO_3$ + 0.2 cc. m/1 Na_2CO_3 + 98 cc. H_2O	1.7 cc. m/1 $NaHCO_3$ + 0.3 cc. m/1 Na_2CO_3 + 98 cc. H_2O	1.6 cc. m/1 $NaHCO_3$ + 0.4 cc. m/1 Na_2CO_3 + 98 cc. H_2O	1.5 cc. m/1 $NaHCO_3$ + 0.5 cc. m/1 Na_2CO_3 + 98 cc. H_2O	1.4 cc. m/1 $NaHCO_3$ + 0.6 cc. m/1 Na_2CO_3 + 98 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.						
5.5	5.18	5.30	5.65	6.00	5.66	5.58	5.97
29	11.52	11.84	12.07	12.56	11.91	12.00	12.35
53	13.05 (1)	13.40 (2)	13.51 (3)	14.00 (4)	13.30 (5)	13.33 (6)	13.75 (7)

Dry weight of gelatin disc.	0.372	0.373	0.375	0.376	0.377	0.377	0.379
Solution	1.3 cc. m/1 $NaHCO_3$ + 0.7 cc. m/1 Na_2CO_3 + 98 cc. H_2O	1.2 cc. m/1 $NaHCO_3$ + 0.8 cc. m/1 Na_2CO_3 + 98 cc. H_2O	1.1 cc. m/1 $NaHCO_3$ + 0.9 cc. m/1 Na_2CO_3 + 98 cc. H_2O	1.0 cc. m/1 $NaHCO_3$ + 1.0 cc. m/1 Na_2CO_3 + 98 cc. H_2O	0.9 cc. m/1 $NaHCO_3$ + 1.1 cc. m/1 Na_2CO_3 + 98 cc. H_2O	0.8 cc. m/1 $NaHCO_3$ + 1.2 cc. m/1 Na_2CO_3 + 98 cc. H_2O	0.7 cc. m/1 $NaHCO_3$ + 1.3 cc. m/1 Na_2CO_3 + 98 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.						
5.5	5.70	6.25	6.40	6.32	6.51	6.18	6.00
29	11.90	12.20	12.22	12.06	12.30	12.16	12.11
53	13.41 (8)	13.47 (9)	13.60 (10)	13.55 (11)	13.71 (12)	13.63 (13)	13.50 (14)

Dry weight of gelatin disc.	0.379	0.379	0.380	0.380	0.380	0.381	0.382
Solution	0.6 cc. m/1 $NaHCO_3$ + 1.4 cc. m/1 Na_2CO_3 + 98 cc. H_2O	0.5 cc. m/1 $NaHCO_3$ + 1.5 cc. m/1 Na_2CO_3 + 98 cc. H_2O	0.4 cc. m/1 $NaHCO_3$ + 1.6 cc. m/1 Na_2CO_3 + 98 cc. H_2O	0.3 cc. m/1 $NaHCO_3$ + 1.7 cc. m/1 Na_2CO_3 + 98 cc. H_2O	0.2 cc. m/1 $NaHCO_3$ + 1.8 cc. m/1 Na_2CO_3 + 98 cc. H_2O	0.1 cc. m/1 $NaHCO_3$ + 1.9 cc. m/1 Na_2CO_3 + 98 cc. H_2O	2.0 cc. m/1 Na_2CO_3 + 98 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.						
5.5	6.50	6.30	6.50	6.34	6.10	6.51	6.35
29	12.60	12.00	12.13	12.16	12.21	12.00	12.35
53	14.01 (15)	13.27 (16)	13.35 (17)	13.52 (18)	13.60 (19)	13.14 (20)	13.50 (21)

TABLE CXVIII—*Concluded*

Dry weight of gelatin disc.	0.382	0.382	0.384	0.384	0.385	0.387	0.388
Solution	1.9 cc. m/1 Na_2CO_3 + 0.1 cc. n/1 NaOH + 98 cc. H_2O	1.8 cc. m/1 Na_2CO_3 + 0.2 cc. n/1 NaOH + 98 cc. H_2O	1.7 cc. m/1 Na_2CO_3 + 0.3 cc. n/1 NaOH + 98 cc. H_2O	1.6 cc. m/1 Na_2CO_3 + 0.4 cc. n/1 NaOH + 98 cc. H_2O	1.5 cc. m/1 Na_2CO_3 + 0.5 cc. n/1 NaOH + 98 cc. H_2O	1.4 cc. m/1 Na_2CO_3 + 0.6 cc. n/1 NaOH + 98 cc. H_2O	1.3 cc. m/1 Na_2CO_3 + 0.7 cc. n/1 NaOH + 98 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.						
5.5	6.92	7.21	7.45	7.40	8.20	8.78	9.80
29	13.01	13.28	13.09	13.78	14.65	15.20	16.34
53	14.26	14.42	14.24	15.02	15.63	16.13	17.24
	(22)	(23)	(24)	(25)	(26)	(27)	(28)

Dry weight of gelatin disc.	0.390	0.390	0.390	0.392	0.393	0.393	0.395
Solution	1.2 cc. m/1 Na_2CO_3 + 0.8 cc. n/1 NaOH + 98 cc. H_2O	1.1 cc. m/1 Na_2CO_3 + 0.9 cc. n/1 NaOH + 98 cc. H_2O	1.0 cc. m/1 Na_2CO_3 + 1.0 cc. n/1 NaOH + 98 cc. H_2O	0.9 cc. m/1 Na_2CO_3 + 1.1 cc. n/1 NaOH + 98 cc. H_2O	0.8 cc. m/1 Na_2CO_3 + 1.2 cc. n/1 NaOH + 98 cc. H_2O	0.7 cc. m/1 Na_2CO_3 + 1.3 cc. n/1 NaOH + 98 cc. H_2O	0.6 cc. m/1 Na_2CO_3 + 1.4 cc. n/1 NaOH + 98 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.						
5.5	9.58	9.93	10.18	10.14	11.85	11.70	11.40
29	16.34	17.51	17.55	17.51	19.84	20.32	20.10
53	17.28	18.51	18.76	18.13	20.45	21.94	21.76
	(29)	(30)	(31)	(32)	(33)	(34)	(35)

Dry weight of gelatin disc.	0.395	0.396	0.396	0.396	0.397	0.397	0.368
Solution	0.5 cc. m/1 Na_2CO_3 + 1.5 cc. n/1 NaOH + 98 cc. H_2O	0.4 cc. m/1 Na_2CO_3 + 1.6 cc. n/1 NaOH + 98 cc. H_2O	0.3 cc. m/1 Na_2CO_3 + 1.7 cc. n/1 NaOH + 98 cc. H_2O	0.2 cc. m/1 Na_2CO_3 + 1.8 cc. n/1 NaOH + 98 cc. H_2O	0.1 cc. m/1 Na_2CO_3 + 1.9 cc. n/1 NaOH + 98 cc. H_2O	2.0 cc. n/1 NaOH + 98 cc. H_2O	100 cc. H_2O
Hours in the solution.	Gain in parts of one part of gelatin.						
5.5	11.86	11.97	11.77	11.75	11.76	13.12	3.36
29	20.64	20.73	20.71	21.72	22.45	24.00	6.23
53	22.50	22.67	22.24	24.90	25.05	29.00	7.18
	(36)	(37)	(38)	(39)	(40)	(41)	(H_2O)

bicarbonate than in pure water and the amount of this swelling increases progressively as we pass from the sodium bicarbonate

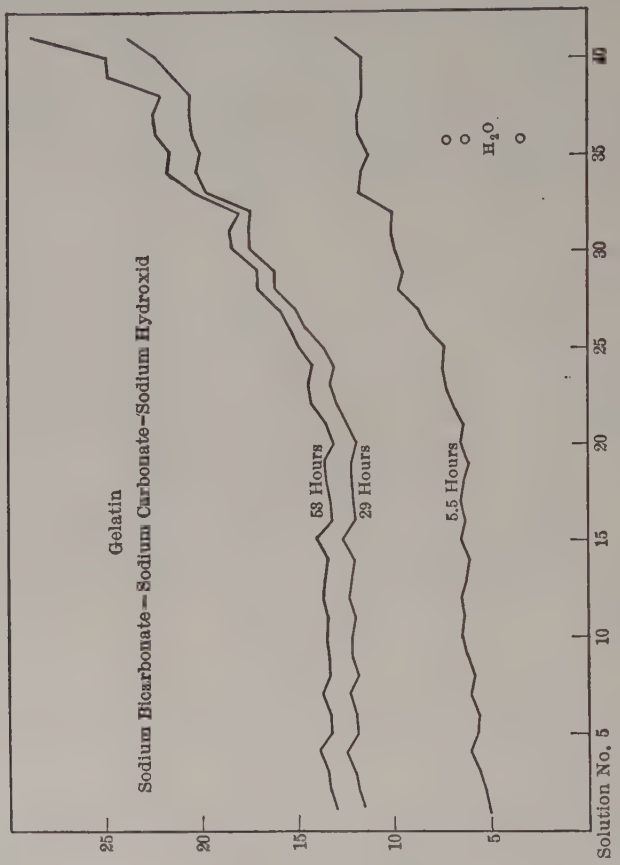


FIGURE 181.

to sodium carbonate and then more abruptly as we enter the realm of the purer sodium hydroxid.

2. On the Liquefaction or "Solution" of Gelatin in Polybasic Acids and their Salts

Since our previous experiments [1] on the liquefaction or "solution" of gelatin in acids or alkalies with or without the simulta-

[1] MARTIN H. FISCHER: Science, **42**, 223 (1915); Kolloid-Zeitschr., **17**, 1 (1915); also see pages 508 and 518; MARTIN H. FISCHER and MARIAN O. HOOKER: Science, **46**, 189 (1917.)

neous presence of various neutral salts might have voiced against them the same criticisms which have been raised against our experiments on swelling, namely, that the effects of the acids and alkalies were not tried out in the presence of " buffer " salts and so could not be applied to the living organism, we ran experiments on the solution of gelatin in parallel with those just described on the swelling of gelatin in various polybasic acids and their salts.[1] As the following experimental facts show, *there is a progressive increase in the tendency of gelatin to go into " solution " in mixtures of the salts of polybasic acids as the amount of acid or alkali in these mixtures is increased from a given low point.*

The same gelatin was used in these experiments as was employed in our previous ones. Its quality was of such high grade that an 0.8 per cent solution of the stock gelatin would set into a solid mass when left to itself for a few hours at 25° C. To make sure of a stiff gelatin mixture we used a concentration well above this, namely, 1 per cent gelatin and set the thermostat for 20° C. It should be added that all the tubes and their contents were treated in exactly the same fashion as to methods of mixing, exposure to heat or other influences which might change temporarily their gelation characteristics, etc.

In Table CXIX are shown the effects of a progressive change from the extreme of a pure phosphoric acid through equimolar concentrations of mono-, di- and trisodium phosphate to pure sodium hydroxid upon the physical state of a fixed amount of gelatin contained in a unit volume of solvent. The maintenance of solidity by the gelatin in the middle of the series with progressive increase in fluidity to the left or to the right of this middle point can be more easily observed in the actual experiments than can be described in words or shown in such a photograph as that of Fig. 182. From so stiff a gelatin that it vibrates when the tube is touched in the middle of the series, we pass through gelatins on either side of this which show the first evidences of a tendency to flow, to the end members which are almost as fluid as thin soup. The change from the solid to the fluid state may be observed in Fig. 182 by noting the line of the meniscus in the tubes; while on slanting the tubes this remains fixed and therefore forms an angle

[1] Martin H. Fischer and Ward D. Coffman: Science, **46**, 189 (1917); Jour. Am. Chem. Soc., **40**, 303 (1918).

TABLE CXIX

GELATIN—*Phosphoric acid through phosphates to sodium hydroxid*

Concentration of solution.	Physical state.
(1) 5 cc. 2% gelatin + 5.0 cc. H_2O (control)	solid
(2) 5 cc. 2% gelatin + 1.0 cc. n/1 H_3PO_4 + 4.0 cc. H_2O	liquid
(3) 5 cc. 2% gelatin + 0.8 cc. n/1 H_3PO_4 + 0.2 cc. m/1 NaH_2PO_4 + 4 cc. H_2O	liquid
(4) 5 cc. 2% gelatin + 0.6 cc. n/1 H_3PO_4 + 0.4 cc. m/1 NaH_2PO_4 + 4 cc. H_2O	semi-solid
(5) 5 cc. 2% gelatin + 0.4 cc. n/1 H_3PO_4 + 0.6 cc. m/1 NaH_2PO_4 + 4 cc. H_2O	semi-solid
(6) 5 cc. 2% gelatin + 0.2 cc. n/1 H_3PO_4 + 0.8 cc. m/1 NaH_2PO_4 + 4 cc. H_2O	solid
(7) 5 cc. 2% gelatin + 1.0 cc. m/1 NaH_2PO_4 + 4.0 cc. H_2O	solid
(8) 5 cc. 2% gelatin + 0.8 cc. m/1 NaH_2PO_4 + 0.2 cc. m/1 Na_2HPO_4 + 4 cc. H_2O	solid
(9) 5 cc. 2% gelatin + 0.6 cc. m/1 NaH_2PO_4 + 0.4 cc. m/1 Na_2HPO_4 + 4 cc. H_2O	solid
(10) 5 cc. 2% gelatin + 0.4 cc. m/1 NaH_2PO_4 + 0.6 cc. m/1 Na_2HPO_4 + 4 cc. H_2O	solid
(11) 5 cc. 2% gelatin + 0.2 cc. m/1 NaH_2PO_4 + 0.8 cc. m/1 Na_2HPO_4 + 4 cc. H_2O	solid
(12) 5 cc. 2% gelatin + 1.0 cc. m/1 Na_2HPO_4 + 4.0 cc. H_2O	solid
(13) 5 cc. 2% gelatin + 0.8 cc. m/1 Na_2HPO_4 + 0.2 cc. m/1 Na_3PO_4 + 4 cc. H_2O	solid
(14) 5 cc. 2% gelatin + 0.6 cc. m/1 Na_2HPO_4 + 0.4 cc. m/1 Na_3PO_4 + 4 cc. H_2O	solid
(15) 5 cc. 2% gelatin + 0.4 cc. m/1 Na_2HPO_4 + 0.6 cc. m/1 Na_3PO_4 + 4 cc. H_2O	semi-solid
(16) 5 cc. 2% gelatin + 0.2 cc. m/1 Na_2HPO_4 + 0.8 cc. m/1 Na_3PO_4 + 4 cc. H_2O	liquid
(17) 5 cc. 2% gelatin + 0.1 cc. m/1 Na_3PO_4 + 4.0 cc. H_2O	liquid
(18) 5 cc. 2% gelatin + 0.8 cc. m/1 Na_3PO_4 + 0.2 cc. n/1 NaOH + 4 cc. H_2O	liquid
(19) 5 cc. 2% gelatin + 0.6 cc. m/1 Na_3PO_4 + 0.4 cc. n/1 NaOH + 4 cc. H_2O	liquid
(20) 5 cc. 2% gelatin + 0.4 cc. m/1 Na_3PO_4 + 0.6 cc. n/1 NaOH + 4 cc. H_2O	liquid
(21) 5 cc. 2% gelatin + 0.2 cc. m/1 Na_3PO_4 + 0.8 cc. n/1 NaOH + 4 cc. H_2O	liquid
(22) 5 cc. 2% gelatin + 1.0 cc. n/1 NaOH + 4 cc. H_2O	liquid

with the horizontal in the middle of the series, it assumes a horizontal position as we approach either end.

Since the concentration of the phosphate in Table CXIX is about ten times that observed, for instance, in the tissues of the human body, we did a second series at a lower concentration of the phosphate and at one more nearly corresponding to physiological conditions. The results so far as maintenance of solidity or liquefaction of the gelatin is concerned are, however, as shown in Table CXX, identical with those previously described in connection with Table CXIX.

As an example of another polybasic acid commonly found in living protoplasm, we chose citric acid, studying its effects by noting the results incident to progressive change from citric acid through mono-, di- and trisodium citrate in equimolar concentrations to pure sodium hydroxid. As shown in Table CXXI and Fig. 183, gelatin again remains solid in the middle of such a series

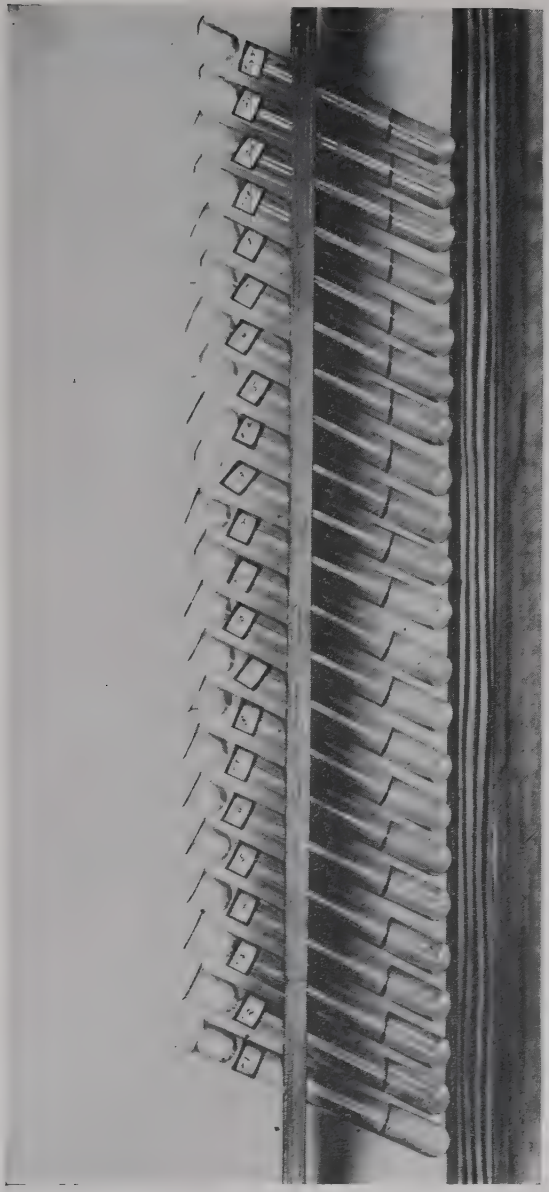


FIGURE 182

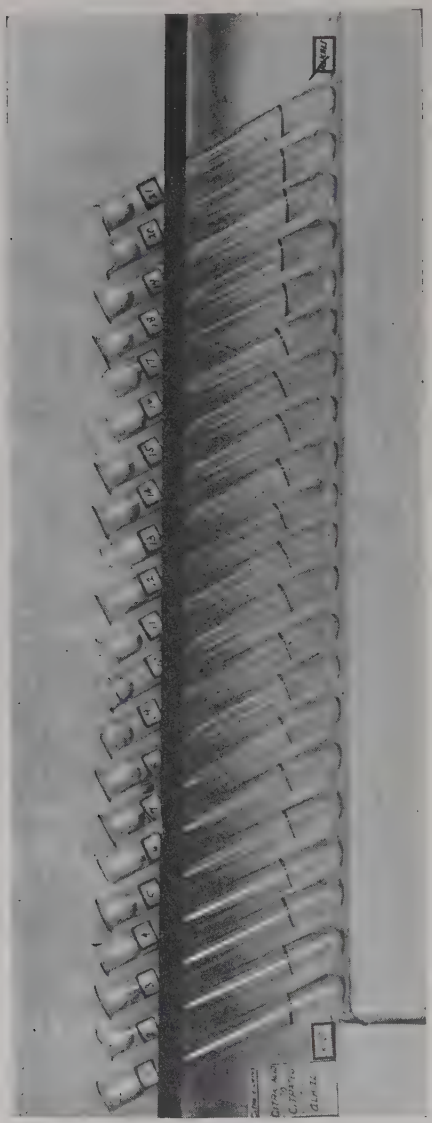


FIGURE 183.

and tends to liquefy as we pass toward the acid or alkaline extreme.

In Table CXXII and Fig. 184 are shown the effects of pro-

TABLE CXX

GELATIN—*Phosphoric acid through phosphates to sodium hydroxid*

Concentration of solution.	Physical state.
(1) 5 cc. 2% gelatin +5.0 cc. H_2O (control)	solid
(2) 5 cc. 2% gelatin +0.10 cc. n/1 H_3PO_4 +4.90 cc. H_2O	liquid
(3) 5 cc. 2% gelatin +0.08 cc. n/1 H_3PO_4 + 0.02 cc. m/1 NaH_2PO_4 + 4.9 cc. H_2O	liquid
(4) 5 cc. 2% gelatin +0.06 cc. n/1 H_3PO_4 + 0.04 cc. m/1 NaH_2PO_4 + 4.9 cc. H_2O	semi-solid
(5) 5 cc. 2% gelatin +0.04 cc. n/1 H_3PO_4 + 0.06 cc. m/1 NaH_2PO_4 + 4.9 cc. H_2O	semi-solid
(6) 5 cc. 2% gelatin +0.02 cc. n/1 H_3PO_4 + 0.08 cc. m/1 NaH_2PO_4 + 4.9 cc. H_2O	solid
(7) 5 cc. 2% gelatin + 0.10 cc. m/1 NaH_2PO_4 + 4.90 cc. H_2O	solid
(8) 5 cc. 2% gelatin +0.08 cc. m/1 NaH_2PO_4 +0.02 cc. m/1 Na_2HPO_4 + 4.9 cc. H_2O	solid
(9) 5 cc. 2% gelatin +0.06 cc. m/1 NaH_2PO_4 +0.04 cc. m/1 Na_2HPO_4 + 4.9 cc. H_2O	solid
(10) 5 cc. 2% gelatin +0.04 cc. m/1 NaH_2PO_4 +0.06 cc. m/1 Na_2HPO_4 + 4.9 cc. H_2O	solid
(11) 5 cc. 2% gelatin +0.02 cc. m/1 NaH_2PO_4 +0.08 cc. m/1 Na_2HPO_4 + 4.9 cc. H_2O	solid
(12) 5 cc. 2% gelatin +0.10 cc. m/1 Na_2HPO_4 +4.90 cc. H_2O	solid
(13) 5 cc. 2% gelatin +0.08 cc. m/1 Na_2HPO_4 +0.02 cc. m/1 Na_3PO_4 + 4.9 cc. H_2O	solid
(14) 5 cc. 2% gelatin +0.06 cc. m/1 Na_2HPO_4 +0.04 cc. m/1 Na_3PO_4 +4.9 cc. H_2O	solid
(15) 5 cc. 2% gelatin +0.04 cc. m/1 Na_2HPO_4 +0.06 cc. m/1 Na_3PO_4 +4.9 cc. H_2O	semi-solid
(16) 5 cc. 2% gelatin +0.02 cc. m/1 Na_2HPO_4 +0.08 cc. m/1 Na_3PO_4 +4.9 cc. H_2O	semi-solid
(17) 5 cc. 2% gelatin +0.10 cc. m/1 Na_3PO_4 +4.90 cc. H_2O	semi-solid
(18) 5 cc. 2% gelatin +0.08 cc. m/1 Na_3PO_4 + 0.02 cc. n/1 NaOH + 4.9 cc. H_2O	liquid
(19) 5 cc. 2% gelatin +0.06 cc. m/1 Na_3PO_4 + 0.04 cc. n/1 NaOH + 4.9 cc. H_2O	liquid
(20) 5 cc. 2% gelatin +0.04 cc. m/1 Na_3PO_4 + 0.06 cc. n/1 NaOH + 4.9 cc. H_2O	liquid
(21) 5 cc. 2% gelatin +0.02 cc. m/1 Na_3PO_4 + 0.08 cc. n/1 NaOH + 4.9 cc. H_2O	liquid
(22) 5 cc. 2% gelatin +0.10 cc. n/1 NaOH +4.9 cc. H_2O	liquid

gressive change from sodium bicarbonate through sodium carbonate to sodium hydroxid. The carbonates in the concentrations indicated in this table showed a greater tendency to liquefy the gelatin than was observed in the phosphate or citrate mixtures previously discussed. To show the effects of the different salt mixtures this series of experiments was therefore kept at a somewhat lower temperature, namely, 5° C. At this temperature the gelatin remains solid in the pure sodium bicarbonate but tends to liquefy as this is replaced by carbonate, or the carbonate by pure sodium hydroxid.

TABLE CXXI

GELATIN—*Citric acid through citrates to sodium hydroxid*

Concentration of solution.	Physical state.
(x) 5 cc. 2% gelatin +5.0 cc. H_2O (control)	solid
(1) 5 cc. 2% gelatin +1.0 cc. n/1 citric acid +4.0 c.c H_2O	liquid
(2) 5 cc. 2% gelatin + 0.8 cc. n/1 citric acid +0.8 cc. m/4 monosodium citrate +3.4 cc. H_2O	semi-solid
(3) 5 cc. 2% gelatin + 0.6 cc. n/1 citric acid + 1.6 cc. m/4 monosodium citrate +2.8 cc. H_2O	solid
(4) 5 cc. 2% gelatin + 0.4 cc. n/1 citric acid + 2.4 cc. m/4 monosodium citrate +2.2 cc. H_2O	solid
(5) 5 cc. 2% gelatin + 0.2 cc. n/1 citric acid + 3.2 cc. m/4 monosodium citrate +1.6 cc. H_2O	solid
(6) 5 cc. 2% gelatin + 4.0 cc. m/4 monosodium citrate +1.0 cc. H_2O	solid
(7) 5 cc. 2% gelatin + 3.2 cc. m/4 monosodium citrate + 0.8 cc. m/4 disodium citrate +1.0 cc. H_2O	solid
(8) 5 cc. 2% gelatin + 2.4 cc. m/4 monosodium citrate + 1.6 cc. m/4 disodium citrate +1.0 cc. H_2O	solid
(9) 5 cc. 2% gelatin + 1.6 cc. m/4 monosodium citrate + 2.4 cc. m/4 disodium citrate +1.0 cc. H_2O	solid
(10) 5 cc. 2% gelatin + 0.8 cc. m/4 monosodium citrate + 3.2 cc. m/4 disodium citrate +1.0 cc. H_2O	solid
(11) 5 cc. 2% gelatin +4.0 cc. m/4 disodium citrate +1.0 cc. H_2O	solid
(12) 5 cc. 2% gelatin +3.2 cc. m/4 disodium citrate +0.8 cc. m/4 trisodium citrate +1.0 cc H_2O	solid
(13) 5 cc. 2% gelatin +2.4 cc. m/4 disodium citrate +1.6 cc. m/4 trisodium citrate +1.0 cc. H_2O	solid
(14) 5 cc. 2% gelatin +1.6 cc. m/4 disodium citrate +2.4 cc. m/4 trisodium citrate +1.0 cc. H_2O	solid
(15) 5 cc. 2% gelatin +0.8 cc. m/4 disodium citrate +3.2 cc. m/4 trisodium citrate +1.0 cc. H_2O	solid
(16) 5 cc. 2% gelatin +4.0 cc. m/4 trisodium citrate +1.0 cc. H_2O	solid
(17) 5 cc. 2% gelatin + 3.2 cc. m/4 trisodium citrate + 0.8 cc. n/1 NaOH +1.0 cc. H_2O	liquid
(18) 5 cc. 2% gelatin + 2.4 cc. m/4 trisodium citrate + 1.6 cc. n/1 NaOH +1.0 cc. H_2O	liquid
(19) 5 cc. 2% gelatin + 1.6 cc. m/4 trisodium citrate + 2.4 cc. n/1 NaOH +1.0 cc. H_2O	liquid
(20) 5 cc. 2% gelatin +0.8 cc. m/4 trisodium citrate +3.2 cc. n/1 NaOH +1.0 cc. H_2O	liquid
(21) 5 cc. 2% gelatin +4.0 cc. n/1 NaOH +1.0 cc. H_2O	liquid

3. On the Swelling of Fibrin in Polybasic Acids and their Salts[1]

In order to show that the swelling (and solution) of gelatin in the presence of so-called "buffer" salts is not exceptional, the following experiments on fibrin were undertaken. They show that the same general law holds for the absorption of water by this protein.

§ 1

The fibrin was a preparation carefully prepared from blood and thoroughly washed to remove as many adhering salts as possible.

[1] MARTIN H. FISCHER and MARTIN BENZINGER: Science, **46**, 189 (1917); Jour. Am. Chem. Soc., **40**, 292 (1918)

After being dried at a low temperature it was pulverized in a mortar. Weighed amounts of the powder (0.5 gram) were then

FIGURE 184.

introduced into definite volumes (20 cc.) of the various solutions employed, contained in calibrated test tubes of uniform diameter

TABLE CXXII

GELATIN—*Sodium bicarbonate through sodium carbonate to sodium hydroxid*

Concentration of solution.	Physical state.
(x) 5 cc. 2% gelatin +5.00 cc. H_2O (control)	solid
(1) 5 cc. 2% gelatin +0.20 cc. m/1 $NaHCO_3$ +4.80 cc. H_2O	solid
(2) 5 cc. 2% gelatin +0.18 cc. m/1 $NaHCO_3$ + 0.02 cc. m/1 Na_2CO_3 + 4.8 cc. H_2O	solid
(3) 5 cc. 2% gelatin +0.16 cc. m/1 $NaHCO_3$ + 0.04 cc. m/1 Na_2CO_3 + 4.8 cc. H_2O	solid
(4) 5 cc. 2% gelatin + 0.14 cc. m/1 $NaHCO_3$ + 0.06 cc. m/1 Na_2CO_3 + 4.8 cc. H_2O	solid
(5) 5 cc. 2% gelatin + 0.12 cc. m/1 $NaHCO_3$ + 0.08 cc. m/1 Na_2CO_3 + 4.8 cc. H_2O	solid
(6) 5 cc. 2% gelatin + 0.10 cc. m/1 $NaHCO_3$ + 0.10 cc. m/1 Na_2CO_3 + 4.8 cc. H_2O	solid
(7) 5 cc. 2% gelatin + 0.08 cc. m/1 $NaHCO_3$ + 0.12 cc. m/1 Na_2CO_3 + 4.8 cc. H_2O	solid
(8) 5 cc. 2% gelatin +0.06 cc. m/1 $NaHCO_3$ + 0.14 cc. m/1 Na_2CO_3 + 4.8 cc. H_2O	solid
(9) 5 cc. 2% gelatin +0.04 cc. m/1 $NaHCO_3$ + 0.16 cc. m/1 Na_2CO_3 + 4.8 cc. H_2O	solid
(10) 5 cc. 2% gelatin + 0.02 cc. m/1 $NaHCO_3$ + 0.18 cc. m/1 Na_2CO_3 + 4.8 cc. H_2O	solid
(11) 5 cc. 2% gelatin +0.20 cc. m/1 Na_2CO_3 +4.80 cc. H_2O	solid
(12) 5 cc. 2% gelatin +0.18 cc. m/1 Na_2CO_3 +0.02 cc. n/1 NaOH +4.8 cc. H_2O	solid
(13) 5 cc. 2% gelatin +0.16 cc. m/1 Na_2CO_3 +0.04 cc. n/1 NaOH +4.8 cc. H_2O	solid
(14) 5 cc. 2% gelatin +0.14 cc. m/1 Na_2CO_3 +0.06 cc. n/1 NaOH +4.8 cc. H_2O	solid
(15) 5 cc. 2% gelatin +0.12 cc. m/1 Na_2CO_3 +0.08 cc. n/1 NaOH +4.8 cc. H_2O	semi-solid
(16) 5 cc. 2% gelatin +0.10 cc. m/1 Na_2CO_3 +0.10 cc. n/1 NaOH +4.8 cc. H_2O	semi-solid
(17) 5 cc. 2% gelatin +0.08 cc. m/1 Na_2CO_3 +0.12 cc. n/1 NaOH +4.8 cc. H_2O	liquid
(18) 5 cc. 2% gelatin +0.06 cc. m/1 Na_2CO_3 +0.14 cc. n/1 NaOH +4.8 cc. H_2O	liquid
(19) 5 cc. 2% gelatin +0.04 cc. m/1 Na_2CO_3 +0.16 cc. n/1 NaOH +4.8 cc. H_2O	liquid
(20) 5 cc. 2% gelatin +0.02 cc. m/1 Na_2CO_3 +0.18 cc. n/1 NaOH +4.8 cc. H_2O	liquid
(21) 5 cc. 2% gelatin +0.20 cc. n/1 NaOH +4.80 cc. H_2O	liquid

(1.5 cm.). The same standard solutions of acids, alkali and of salts as were employed in the study of gelatin were used. All the mixtures in the various tubes were treated in exactly the same fashion, as to shaking, settling, etc. The height of the swollen fibrin columns, at the end of 24 hours was taken as the index of water absorption. The results of our several series of experiments may be summed up as follows:

(*a*) We tested first the effects of a progressive change from monosodium citrate through disodium citrate to trisodium citrate in equimolar concentrations, continuing the series toward a pure

acid on the one side and toward a pure alkali upon the other side, as shown in Table CXXIII.

As indicated by the heights of the fibrin columns, and better by the curve of Fig. 185 which expresses the results of this experiment graphically, greatest swelling is observed in the pure solutions of acid or alkali. From these extremes the amount of swell-

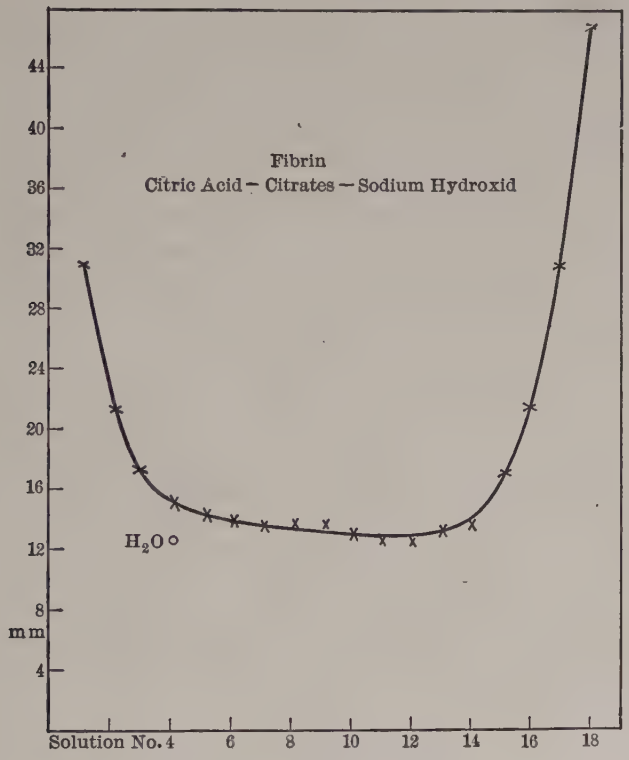


FIGURE 185.

ing decreases as neutralization progresses until a low point is reached in the middle of the curve. This low point is observed in a mixture of, approximately, one molar equivalent of monosodium citrate with two molar equivalents of disodium citrate. In comparing this minimal point for fibrin with that obtained in the case of gelatin it is seen that in the latter instance it lies closer to the (theoretically) pure solution of monosodium citrate.

TABLE CXXIII

FIBRIN—*Citric acid through citrates to sodium hydroxid*

Concentration of solution.	Height of fibrin column in mm. after 24 hours.
(1) 2.0 cc. n/1 citric acid +18 cc. H_2O	31.0
(2) 1.6 cc. n/1 citric acid +0.4 cc. m/1 monosodium citrate +18 cc. H_2O	21.5
(3) 1.2 cc. n/1 citric acid +0.8 cc. m/1 monosodium citrate +18 cc. H_2O	16.5
(4) 0.8 cc. n/1 citric acid +1.2 cc. m/1 monosodium citrate +18 cc. H_2O	15.0
(5) 0.4 cc. n/1 citric acid +1.6 cc. m/1 monosodium citrate +18 cc. H_2O	14.0
(6) 2.0 cc. m/1 monosodium citrate +18 cc. H_2O	14.0
(7) 1.6 cc. m/1 monosodium citrate +0.4 cc. m/1 disodium citrate +18 cc. H_2O	13.5
(8) 1.2 cc. m/1 monosodium citrate +0.8 cc. m/1 disodium citrate +18 cc. H_2O	13.5
(9) 0.8 cc. m/1 monosodium citrate +1.2 cc. m/1 disodium citrate +18 cc. H_2O	13.5
(10) 0.4 cc. m/1 monosodium citrate +1.6 cc. m/1 disodium citrate +18 cc. H_2O	13.0
(11) 2.0 cc. m/1 disodium citrate +18 cc. H_2O	12.5
(12) 1.6 cc. m/1 disodium citrate +0.4 cc. m/1 trisodium citrate +18 cc. H_2O	12.5
(13) 1.2 cc. m/1 disodium citrate +0.8 cc. m/1 trisodium citrate +18 cc. H_2O	13.0
(14) 0.8 cc. m/1 disodium citrate +1.2 cc. m/1 trisodium citrate +18 cc. H_2O	13.5
(15) 0.4 cc. m/1 disodium citrate +1.6 cc. m/1 trisodium citrate +18 cc. H_2O	17.0
(16) 2.0 cc. m/1 trisodium citrate +18 cc. H_2O	21.5
(17) 1.6 cc. m/1 trisodium citrate +0.4 cc. n/1 NaOH +18 cc. H_2O	31.0
(18) 1.2 cc. m/1 trisodium citrate +0.8 cc. n/1 NaOH +18 cc. H_2O	47.0
(19) 0.8 cc. m/1 trisodium citrate +1.2 cc. n/1 NaOH +18 cc. H_2O	58.0
(20) 0.4 cc. m/1 trisodium citrate +1.6 cc. n/1 NaOH +18 cc. H_2O	73.0
(21) 2.0 cc. n/1 NaOH +18 cc. H_2O	96.5
(22) 20 cc. water (control)	12.5

(*b*) In a next series of experiments we tested the effects of a gradual increase in the phosphoric acid content of a solution con-

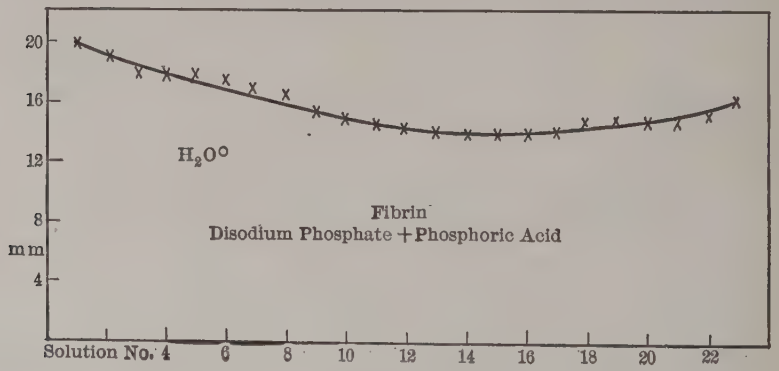


FIGURE 186.

taining a fixed amount of disodium phosphate. The results are shown in Table CXXIV and Fig. 186. When phosphoric acid is added to disodium phosphate there is at first a decrease in the

TABLE CXXIV

FIBRIN—*Disodium phosphate+increasing amounts of phosphoric acid*

Concentration of solution.	Height of fibrin column in mm. after 24 hours.
(1) 0.8 cc. m/4 Na_2HPO_4+0.44 cc. n/1 H_3PO_4+18.76 cc. H_2O	20.0
(2) 0.8 cc. m/4 Na_2HPO_4+0.42 cc. n/1 H_3PO_4+18 78 cc. H_2O	19.0
(3) 0.8 cc. m/4 Na_2HPO_4+0.40 cc. n/1 H_3PO_4+18.80 cc. H_2O	18.0
(4) 0.8 cc. m/4 Na_2HPO_4+0.38 cc. n/1 H_3PO_4+18.82 cc. H_2O	18.0
(5) 0.8 cc. m/4 Na_2HPO_4+0.36 cc. n/1 H_3PO_4+18.84 cc. H_2O	18.0
(6) 0.8 cc. m/4 Na_2HPO_4+0.34 cc. n/1 H_3PO_4+18.86 cc. H_2O	17.5
(7) 0.8 cc. m/4 Na_2HPO_4+0.32 cc. n/1 H_3PO_4+18.88 cc. H_2O	17.0
(8) 0.8 cc. m/4 Na_2HPO_4+0.30 cc. n/1 H_3PO_4+18.90 cc. H_2O	16.5
(9) 0.8 cc. m/4 Na_2HPO_4+0.28 cc. n/1 H_3PO_4+18.92 cc. H_2O	15.5
(10) 0.8 cc. m/4 Na_2HPO_4+0.26 cc. n/1 H_3PO_4+18.94 cc. H_2O	15.0
(11) 0.8 cc. m/4 Na_2HPO_4+0.24 cc. n/1 H_3PO_4+18.96 cc. H_2O	14.5
(12) 0.8 cc. m/4 Na_2HPO_4+0.22 cc. n/1 H_3PO_4+18.98 cc. H_2O	14.0
(13) 0.8 cc. m/4 Na_2HPO_4+0.20 cc. n/1 H_3PO_4+19.00 cc. H_2O	14.0
(14) 0.8 cc. m/4 Na_2HPO_4+0.18 cc. n/1 H_3PO_4+19.02 cc. H_2O	14.0
(15) 0.8 cc. m/4 Na_2HPO_4+0.16 cc. n/1 H_3PO_4+19.04 cc. H_2O	13.5
(16) 0.8 cc. m/4 Na_2HPO_4+0.14 cc. n/1 H_3PO_4+19.06 cc. H_2O	14.0
(17) 0.8 cc m/4 Na_2HPO_4+0.12 cc. n/1 H_3PO_4+19.08 cc. H_2O	14.0
(18) 0.8 cc. m/4 Na_2HPO_4+0.10 cc. n/1 H_3PO_4+19.10 cc. H_2O	14.5
(19) 0.8 cc. m/4 Na_2HPO_4+0.08 cc. n/1 H_3PO_4+19.12 cc. H_2O	14.5
(20) 0.8 cc. m/4 Na_2HPO_4+0.06 cc. n/1 H_3PO_4+19.14 cc. H_2O	14.5
(21) 0.8 cc. m/4 Na_2HPO_4+0.04 cc. n/1 H_3PO_4+19.16 cc. H_2O	14.5
(22) 0.8 cc. m/4 Na_2HPO_4+0.02 cc. n/1 H_3PO_4+19.18 cc. H_2O	15.5
(23) 0.8 cc. m/4 Na_2HPO_4+19.2 cc. H_2O	16.0
(24) 20 cc. water (control)	12.5

amount of swelling. This gives way later to an increased swelling as the concentration of the acid passes a certain point. The experimental results show that this point of minimal swelling is observed in a mixture which theoretically is composed of about molar equivalents of disodium phosphate and monosodium phosphate.

(*c*) In Table CXXV and Fig. 187 are shown the effects of adding to the same concentration of disodium phosphate used in the previous experiment, progressively greater amounts of sodium hydroxid. There is, with every increase in the concentration of the added alkali, an increase in the height of the swelling column.

(*d*) The effects of adding progressively greater amounts of sodium hydroxid to a fixed amount of monosodium phosphate of the same molar concentration as the disodium phosphate used in the previous experiments are shown in Table CXXVI and Fig. 188. When small amounts of the alkali are added to the monosodium phosphate there is to be observed at first a decrease in the

TABLE CXXV

FIBRIN—*Disodium phosphate+increasing amounts of sodium hydroxid*

Concentration of solution.	Height of fibrin column in mm. after 24 hours.
(1) 0.8 cc. m/4 Na_2HPO_4+19.2 cc. H_2O	16.0
(2) 0.8 cc. m/4 Na_2HPO_4+ 0.02 cc. n/1 NaOH+19.18 cc. H_2O	16.5
(3) 0.8 cc. m/4 Na_2HPO_4+ 0.04 cc. n/1 NaOH+19.16 cc. H_2O	17.5
(4) 0.8 cc. m/4 Na_2HPO_4+ 0.06 cc. n/1 NaOH+19.14 cc. H_2O	18.5
(5) 0.8 cc. m/4 Na_2HPO_4+ 0.08 cc. n/1 NaOH+19.12 cc. H_2O	19.5
(6) 0.8 cc. m/4 Na_2HPO_4+ 0.10 cc. n/1 NaOH+19.10 cc. H_2O	21.0
(7) 0.8 cc. m/4 Na_2HPO_4+ 0.12 cc. n/1 NaOH+19.08 cc. H_2O	22.0
(8) 0.8 cc. m/4 Na_2HPO_4+ 0.14 cc. n/1 NaOH+19.06 cc. H_2O	23.0
(9) 0.8 cc. m/4 Na_2HPO_4+ 0.16 cc. n/1 NaOH+19.04 cc. H_2O	24.5
(10) 0.8 cc. m/4 Na_2HPO_4+ 0.18 cc. n/1 NaOH+19.02 cc. H_2O	26.5
(11) 0.8 cc m/4 Na_2HPO_4+ 0.20 cc. n/1 NaOH+19.00 cc. H_2O	29.5
(12) 0.8 cc. m/4 Na_2HPO_4+ 0.22 cc. n/1 NaOH+18.98 cc. H_2O	34.5
(13) 20 cc. water (control)	12.5

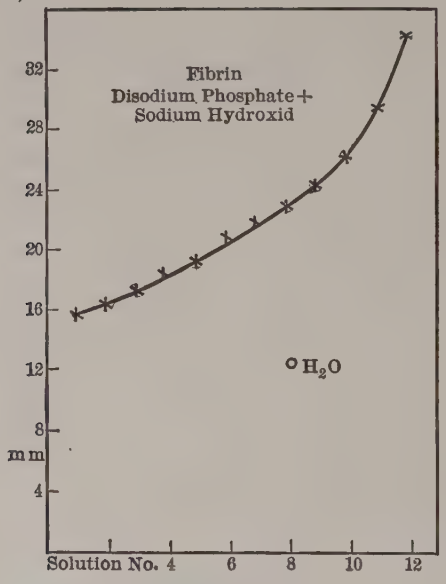


FIGURE 187.

amount of swelling which later, however, with further increase in the amount of alkali added, gives way to an increased swelling. It is again obvious that the low point in the swelling curve is found

TABLE CXXVI

FIBRIN—*Monosodium phosphate+increasing amounts of sodium hydroxid*

Concentration of solution.	Height of fibrin column in mm. after 24 hours.
(1) 0.2 cc. m/1 NaH_2PO_4+19.80 cc. H_2O	16.0
(2) 0.2 cc. m/1 NaH_2PO_4+ 0.02 cc. n/1 NaOH+19.78 cc. H_2O	15.5
(3) 0.2 cc. m/1 NaH_2PO_4+ 0.04 cc. n/1 NaOH+19.76 cc. H_2O	15.5
(4) 0.2 cc. m/1 NaH_2PO_4+ 0.06 cc. n/1 NaOH+19.74 cc. H_2O	15.5
(5) 0.2 cc. m/1 NaH_2PO_4+ 0.08 cc. n/1 NaOH+19.72 cc. H_2O	15.0
(6) 0.2 cc. m/1 NaH_2PO_4+ 0.10 cc. n/1 NaOH+19.70 cc. H_2O	15.0
(7) 0.2 cc. m/1 NaH_2PO_4+ 0.12 cc. n/1 NaOH+19.68 cc. H_2O	14.0
(8) 0.2 cc. m/1 NaH_2PO_4+ 0.14 cc. n/1 NaOH+19.66 cc. H_2O	15.0
(9) 0.2 cc. m/1 NaH_2PO_4+ 0.16 cc. n/1 NaOH+19.64 cc. H_2O	15.5
(10) 0.2 cc. m/1 NaH_2PO_4+ 0.18 cc. n/1 NaOH+19.62 cc. H_2O	15.5
(11) 0.2 cc. m/1 NaH_2PO_4+ 0.20 cc. n/1 NaOH+19.60 cc. H_2O	15.5
(12) 0.2 cc. m/1 NaH_2PO_4+ 0.22 cc. n/1 NaOH+19.58 cc. H_2O	16.0
(13) 0.2 cc. m/1 NaH_2PO_4+ 0.24 cc. n/1 NaOH+19.56 cc. H_2O	16.5
(14) 0.2 cc. m/1 NaH_2PO_4+ 0.26 cc. n/1 NaOH+19.54 cc. H_2O	18.0
(15) 0.2 cc. m/1 NaH_2PO_4+ 0.28 cc. n/1 NaOH+19.52 cc. H_2O	19.5
(16) 0.2 cc. m/1 NaH_2PO_4+ 0.30 cc. n/1 NaOH+19.50 cc. H_2O	21.5
(17) 0.2 cc. m/1 NaH_2PO_4+ 0.32 cc. n/1 NaOH+19.48 cc. H_2O	23.5
(18) 0.2 cc. m/1 NaH_2PO_4+ 0.34 cc. n/1 NaOH+19.46 cc. H_2O	25.0
(19) 0.2 cc. m/1 NaH_2PO_4+ 0.36 cc. n/1 NaOH+19.44 cc. H_2O	27.5
(20) 0.2 cc. m/1 NaH_2PO_4+ 0.38 cc. n/1 NaOH+19.42 cc H_2O	33.0
(21) 20 cc. water (control)	12.5

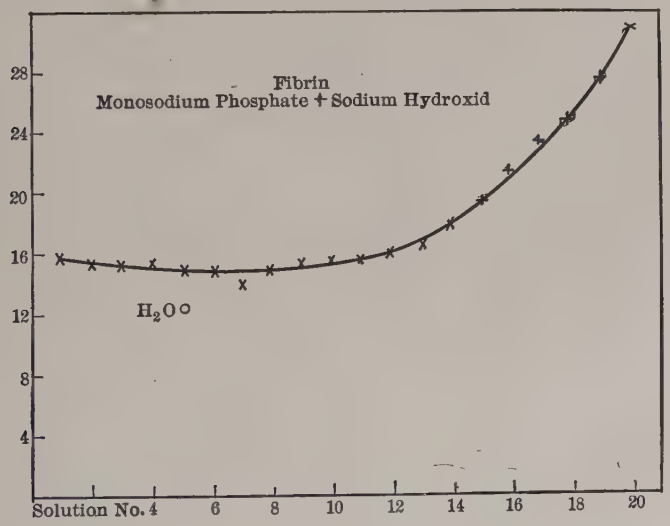


FIGURE 188.

at a point at which the mixture is essentially one of molar equivalents of monosodium and disodium phosphate.

TABLE CXXVII

FIBRIN—*Phosphoric acid+increasing amounts of sodium hydroxid*

Concentration of solution.	Height of fibrin column in mm. after 24 hours.
(1) 0.6 cc. n/1 H_3PO_4+0.02 cc. n/1 NaOH+19.38 cc. H_2O	16.5
(2) 0.6 cc. n/1 H_3PO_4+0.04 cc. n/1 NaOH+19.36 cc. H_2O	15.5
(3) 0.6 cc. n/1 H_3PO_4+0.06 cc. n/1 NaOH+19.34 cc. H_2O	15.0
(4) 0.6 cc. n/1 H_3PO_4+0.08 cc. n/1 NaOH+19.32 cc. H_2O	14.5
(5) 0.6 cc. n/1 H_3PO_4+0.10 cc. n/1 NaOH+19.30 cc. H_2O	14.0
(6) 0.6 cc. n/1 H_3PO_4+0.12 cc. n/1 NaOH+19.28 cc. H_2O	13.0
(7) 0.6 cc. n/1 H_3PO_4+0.14 cc. n/1 NaOH+19.26 cc. H_2O	12.5
(8) 0.6 cc. n/1 H_3PO_4+0.16 cc. n/1 NaOH+19.24 cc. H_2O	12.5
(9) 0.6 cc. n/1 H_3PO_4+0.18 cc. n/1 NaOH+19.22 cc. H_2O	12.5
(10) 0.6 cc. n/1 H_3PO_4+0.20 cc. n/1 NaOH+19.20 cc. H_2O	12.5
(11) 0.6 cc. n/1 H_3PO_4+0.22 cc. n/1 NaOH+19.18 cc. H_2O	12.5
(12) 0.6 cc. n/1 H_3PO_4+0.24 cc. n/1 NaOH+19.16 cc. H_2O	12.5
(13) 0.6 cc. n/1 H_3PO_4+0.26 cc. n/1 NaOH+19.14 cc. H_2O	12.5
(14) 0.6 cc. n/1 H_3PO_4+0.28 cc. n/1 NaOH+19.12 cc. H_2O	12.5
(15) 0.6 cc. n/1 H_3PO_4+0.30 cc. n/1 NaOH+19.10 cc. H_2O	12.5
(16) 0.6 cc. n/1 H_3PO_4+0.32 cc. n/1 NaOH+19.08 cc. H_2O	12.5
(17) 0.6 cc. n/1 H_3PO_4+0.34 cc. n/1 NaOH+19.06 cc. H_2O	12.5
(18) 0.6 cc. n/1 H_3PO_4+0.36 cc. n/1 NaOH+19.04 cc. H_2O	12.5
(19) 0.6 cc. n/1 H_3PO_4+0.38 cc. n/1 NaOH+19.02 cc. H_2O	12.5
(20) 0.6 cc. n/1 H_3PO_4+0.40 cc. n/1 NaOH+19.00 cc. H_2O	13.0
(21) 0.6 cc. n/1 H_3PO_4+0.42 cc. n/1 NaOH+18.98 cc. H_2O	14.5
(22) 0.6 cc. n/1 H_3PO_4+0.44 cc. n/1 NaOH+18.96 cc. H_2O	15.0
(23) 0.6 cc. n/1 H_3PO_4+0.46 cc. n/1 NaOH+18.94 cc. H_2O	16.0
(24) 0.6 cc. n/1 H_3PO_4+0.48 cc. n/1 NaOH+18.92 cc. H_2O	17.0
(25) 0.6 cc. n/1 H_3PO_4+0.50 cc. n/1 NaOH+18.90 cc. H_2O	75.0(?)
(26) 0.6 cc. n/1 H_3PO_4+0.52 cc. n/1 NaOH+18.88 cc. H_2O	17.5
(27) 0.6 cc. n/1 H_3PO_4+0.54 cc. n/1 NaOH+18.86 cc. H_2O	17.5
(28) 0.6 cc. n/1 H_3PO_4+0.56 cc. n/1 NaOH+18.84 cc. H_2O	18.0
(29) 0.6 cc. n/1 H_3PO_4+0.58 cc. n/1 NaOH+18.82 cc. H_2O	20.0
(30) 0.6 cc. n/1 H_3PO_4+0.60 cc. n/1 NaOH+18.80 cc. H_2O	26.0
(31) 0.6 cc. n/1 H_3PO_4+0.62 cc. n/1 NaOH+18.78 cc. H_2O	30.0
(32) 0.6 cc. n/1 H_3PO_4+0.64 cc. n/1 NaOH+18.76 cc. H_2O	24.0
(33) 20 cc. water (control)	12.5

(*e*) The results of another type of variation in experimental procedure is shown in Table CXXVII and Fig. 189. Here a fixed amount of phosphoric acid has added to it progressively greater amounts of sodium hydroxid. This arrangement allows us to see the effects of simultaneously reducing acid content while increasing the amount and kind of phosphate present. The result is again, however, a curve of the same general type already discussed. Beginning with the greatest swelling in the pure acid there is a gradual fall in the curve until a low point is reached in a mixture lying midway between the (theoretically) pure monosodium phosphate and the pure disodium phosphate.

(*f*) A final type of variation in experimental procedure is shown in Table CXXVIII and Fig. 190. Here a fixed amount

of alkali has added to it progressively greater amounts of phosphoric acid until neutralization is carried to the point of get-

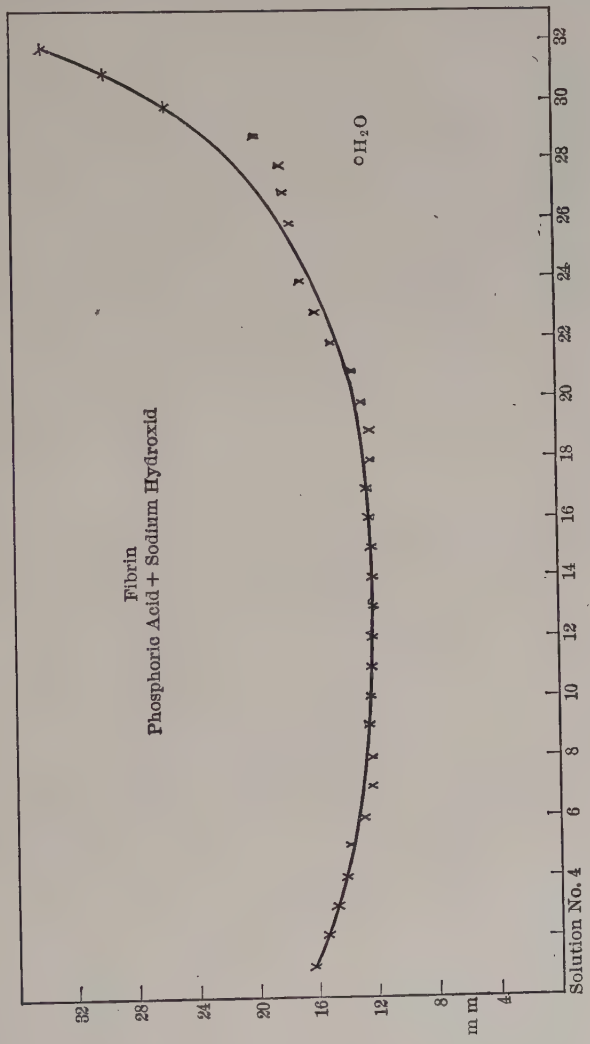


FIGURE 189.

ting a (theoretically) pure solution of trisodium phosphate. The progressive decrease in the amount of swelling with decrease in alkalinity and increase in phosphate content is readily apparent.

TABLE CXXVIII

FIBRIN—*Sodium hydroxid+increasing amounts of phosphoric acid*

Concentration of solution.	Height of fibrin column in mm. after 24 hours.
(1) 0.6 cc. n/1 NaOH +0.60 cc. n/1 H_3PO_4 +18.80 cc. H_2O	23.0
(2) 0.6 cc. n/1 NaOH +0.58 cc. n/1 H_3PO_4 +18.82 cc. H_2O	23.5
(3) 0.6 cc. n/1 NaOH +0.54 cc. n/1 H_3PO_4 +18.86 cc. H_2O	25.5
(4) 0.6 cc. n/1 NaOH +0.50 cc. n/1 H_3PO_4 +18.90 cc. H_2O	28.0
(5) 0.6 cc. n/1 NaOH +0.46 cc. n/1 H_3PO_4 +18.94 cc. H_2O	32.5
(6) 0.6 cc. n/1 NaOH +0.42 cc. n/1 H_3PO_4 +18.98 cc. H_2O	35.5
(7) 0.6 cc. n/1 NaOH +0.38 cc. n/1 H_3PO_4 +19.02 cc. H_2O	40.5
(8) 0.6 cc. n/1 NaOH +0.34 cc. n/1 H_3PO_4 +19.06 cc. H_2O	41.0
(9) 0.6 cc. n/1 NaOH +0.30 cc. n/1 H_3PO_4 +19.10 cc. H_2O	45.0
(10) 0.6 cc. n/1 NaOH +0.26 cc. n/1 H_3PO_4 +19.14 cc. H_2O	47.5
(11) 0.6 cc. n/1 NaOH +0.22 cc. n/1 H_3PO_4 +19.18 cc. H_2O	52.0
(12) 0.6 cc. n/1 NaOH +0.18 cc. n/1 H_3PO_4 +19.22 cc. H_2O	59.0
(13) 0.6 cc. n/1 NaOH +0.14 cc. n/1 H_3PO_4 +19.26 cc. H_2O	62.0
(14) 0.6 cc. n/1 NaOH +0.10 cc. n/1 H_3PO_4 +19.30 cc. H_2O	63.5
(15) 0.6 cc. n/1 NaOH +0.06 cc. n/1 H_3PO_4 +19.34 cc. H_2O	68.0
(16) 0.6 cc. n/1 NaOH +0.02 cc. n/1 H_3PO_4 +19.38 cc. H_2O	75.0
(17) 20 cc. water (control)	12.5

§ 2

The experimental findings detailed in these paragraphs with those previously outlined for gelatin, bring out the fact that the minimal points of water absorption in citrate and phosphate mixtures are different for the two proteins. While the minimal swelling point for gelatin is found in a mixture closely approximating one of pure monosodium citrate or pure monosodium phosphate, the minimal one for fibrin is found at a point represented more nearly by a mixture of molar equivalents of the mono- and disalts of these two acids. Such differences in the behavior of various proteins must be kept in mind when these experiments on simple protein colloids are applied to biological material. Protoplasm represents, according to present beliefs, a mixture of at least two and probably several different proteins.

We hold that these results on fibrin with those already detailed on the swelling of gelatin in polybasic acids and their salts, corroborate and amplify the ideas previously expressed regarding the importance of acids, of alkalies, of various salts, and of these in mixture in determining the amount of water absorbed by protoplasm under physiological and pathological conditions. The well-established qualitative and quantitative analogies between the absorption of water by various hydrophilic colloids

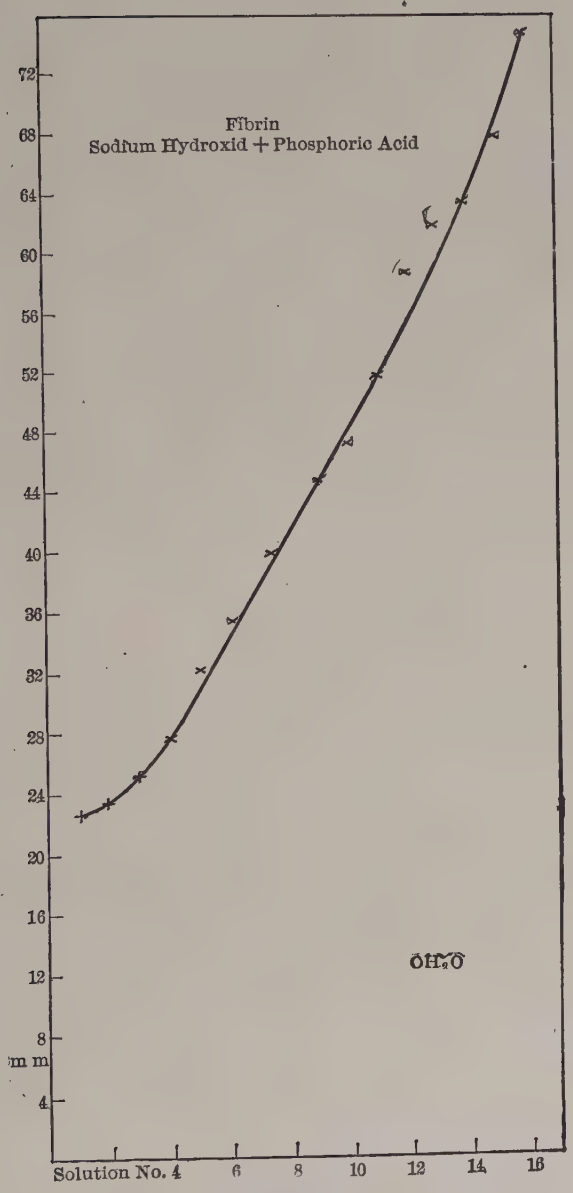

Fibrin
Sodium Hydroxid + Phosphoric Acid
72
68
64
60
56
52
48
44
40
36
32
28
24
20
16
12
8
4
m m
Solution No. 4
6
8
10
12
14
16

FIGURE 190.

(like the proteins) and isolated cells, organs or organisms, whether of animal or vegetable origin, show that the problem of water absorption is essentially a colloid-chemical phenomenon. These studies with polybasic acids and their salts permit us to re-emphasize the importance of an abnormal production or accumulation of acids within such colloid systems for increasing the amount of water thus held and this independently of the fact that such accumulation of acid may occur in the presence or in the absence of so-called "buffer" salts.[1] Through the accumulation or production in protoplasm of an abnormally great amount of acid (or of alkali), we are thus enabled to explain the mechanism by which the abnormally high hydrations of living cells are brought about as such are observed in the excessive turgors of plant tissues, in the œdemas which involve the animal body, or in those "diseases" now to be discussed which are in essence only œdemas of certain organs, like nephritis (œdema of the kidney), glaucoma (œdema of the eye) or "uremia" (œdema of the brain).

VIII

ON THE ALLEGED CONSEQUENCES OF KIDNEY DISEASE

We need again to break into our main argument here showing how the factor of acid production acting upon the colloids of the kidney leads to the signs and symptoms of nephritis to discuss the alleged consequences of kidney disease. Until we have disposed of this question we shall not be of one mind on certain points where agreement must be reached before progress can be made. *Many of the clinical manifestations observed in patients having kidney disease are considered consequences of the impaired kidney function. There are consequences to such impairment, but almost without exception all those most generally regarded as such do not belong in the group.* Dogmatic teaching and the inertia of time have woven here a tangled skein, but if we will consider these alleged consequences separately and logically, order can easily be established.

[1] L. J. Henderson (Jour. Am. Chem. Soc., **40**, 857 (1918)) is still unconvinced of this. My reply to his criticisms, for which there is not space in this volume, may be found in Jour. Am. Chem. Soc., **40**, 862 (1918).

1. On the Relation of Vascular Disease to Nephritis

§ 1

It has long been recognized that vascular disease, increased blood pressure and cardiac hypertrophy are frequently associated with changes in the kidney which in the aggregate lead to the morphological picture which we call chronic interstitial nephritis. It is also quite generally accepted that such blood vessel disease, hypertrophy and increased blood pressure are consequent upon the kidney disease in the sense that impairment of function is supposed to permit poisonous substances to accumulate in the blood, which in addition to producing destructive lesions in the blood vessels themselves lead also to the cardiac hypertrophy and high blood pressure. This conception with all its various modifications is fundamentally wrong. Neither logic nor experiment support it and everything argues against it. *The primary disturbance in chronic interstitial nephritis associated with vascular disease and changes in the heart is the vascular disease, and the changes in the kidneys, in the heart and in the other organs of the body are secondary to it.*

No one has as yet produced in animals a chronic interstitial nephritis associated with vascular disease and a hypertrophy of the heart. By injecting various poisons into animals, such as the salts of the heavy metals, it has been possible to produce a chronic interstitial type of nephritis, but the animals show no changes in their vascular system and no hypertrophy of the heart. These kidneys really correspond to the chronic interstitial types of nephritis which we see in human beings who have passed through a generalized parenchymatous nephritis due to an intoxication of some sort and in whom pieces of the kidney have been lost with secondary contracture. We do not as yet possess any experimental method of producing in animals vascular disease as observed in man and not until we do, need we expect to observe a cardiac hypertrophy, increased blood pressure and destructive lesions in the kidney which correspond with the changes observed in human beings.

The current notion that vascular change, high blood pressure, etc., are secondary to kidney disease can easily be tested out experimentally. When we observe such signs and symptoms

in a human being, the patient is, of course, still alive. He must in consequence have sufficient kidney substance available to live. It is an easy matter experimentally to reduce the kidney substance of an animal down to the physiological minimum. If the current opinions were correct such animals should show vascular changes, high blood pressure and cardiac hypertrophy, but as a matter of fact they show none of them. In Figs. 191, 192, and 193 are shown the photographs of a series of rabbits in which the kidney substance was thus reduced. A wedge was first taken out of one kidney so as to reduce its volume one-

FIGURE 191.

half or even more, and then after complete recovery from the effects of this operation the whole of the opposite kidney was removed. The animals had therefore but one-fourth to one-eighth their total kidney substance left. We kept these animals in the laboratory for more than five years—a period which easily represents over two-thirds their total life expectancy. They constituted our breeding stock and were perfectly normal until accidentally killed by a bulldog which got at large. In Fig. 191 are shown three breeding males, in Figs. 192 and 193 two mothers of this series with their families.

Lest it be thought that such facts hold only for the herbivora the following facts regarding some dogs and rats which had a

similar reduction in kidney tissue and which were none the worse for it are of interest. "Nellie," a mongrel pup, suffered a removal of one-third her right kidney April 9, 1913. The whole of the opposite kidney was removed May 19, 1913. After having had a family in the interim, this dog was exhibited as a normal creature (see Fig. 194) at the scientific exhibit of the American Medical Association in San Francisco in 1915. She continued well, mothering three further litters (see Fig. 195) until May 8, 1919, when she died of intestinal obstruction due to a hernia of the ileum into the left kidney wound. Save for a transverse scar the remaining

FIGURE 192

fraction of kidney was normal and there were no changes in the heart or blood vessels.

"Blackie," a young mongrel dog, had one half her right kidney removed October 10, 1914, and the whole of the opposite one November 10. This dog is still alive (October 16, 1920) and well, having had some half dozen litters in the meantime, two of which (photographed respectively March 20, 1918, and October 20, 1918) are shown with the mother in Figs. 196 and 197.

Rats also continue entirely normal after removal of three-quarters their total kidney substance. We have kept both male and female rats thus operated upon (Figs. 198 and 199) for more than two years in the laboratory which covers the major portion

of their life expectancy. In spite of the type of food fed (we kept large numbers on a purely "meat" diet) none of the animals ever showed any changes in their vascular system.

There is only one way in which the results of these experiments

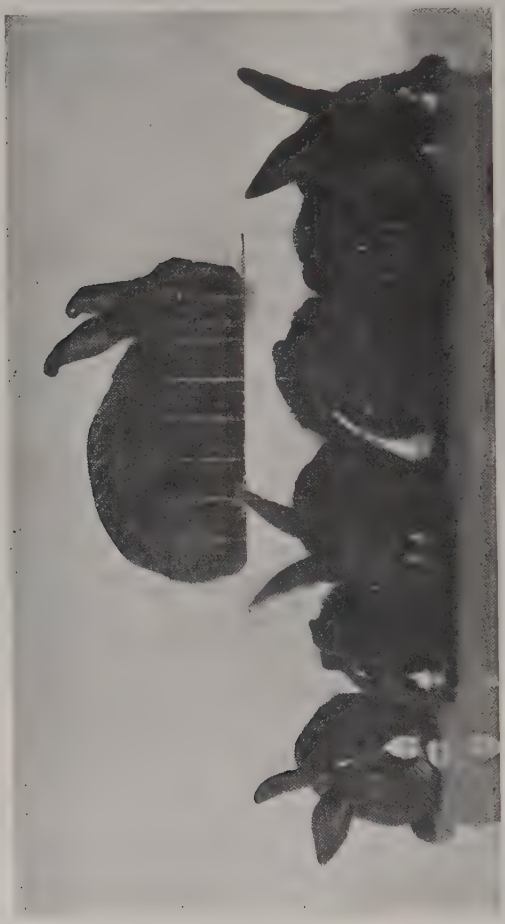


FIGURE 193.

can be interpreted. *Loss of kidney function does not lead to vascular disease and cardiac hypertrophy, nor to the high blood pressure or the other signs so frequently attributed to chronic interstitial nephritis.*

Once we begin to look upon the vascular disease as the primary cause of the nephritis, the cardiac hypertrophy, etc., we encoun-

ter no difficulty in interpreting these. As is well known, the primary changes in vascular disease occur in the smaller blood vessels. When vascular disease attacks the large blood vessels it is through the small blood vessels which supply their coats. In consequence of the (thrombotic) changes occurring in the small vessels circumscribed areas situated in the large blood vessels suffer swelling, fatty changes, softening and scarring. The mixture constitutes the ordinary picture of vascular "degen-

FIGURE 194.

eration." As similar (thrombotic) changes occur in the various organs, the spots thus deprived of a proper blood supply also "degenerate." If the attack happens to be made upon the kidney, spots of dying kidney tissue appear scattered through an otherwise healthy-looking kidney. This is the picture of chronic interstitial nephritis associated with vascular disease, in which pathological entity it is always the rule to find the greatest variety of morphological changes. While certain regions are entirely normal in appearance, others show characteristic "degenerative"

FIGURE 195

FIGURE 196.

changes, as evidenced by the presence of cells that are swollen and granular, or perhaps have lost their nuclei and are disintegrated (*localized* parenchymatous nephritis). To take the place of the dead cells we may find new parenchyma cells form-

FIGURE 197.

ing, or there may be evidences of connective tissue proliferation, indicating the ultimate formation of a scar.

This patchy appearance, resulting from a mixture of normal, degenerating and regenerating cellular elements in the kidney, stands in marked contrast to the uniformity of appearance presented by a kidney that has been poisoned, say, with the toxins of an acute infectious disease. Here in a certain sense, all parts of the kidney are affected and to about the same degree. The appearances correspond with the fact that in the first case small patches of the kidneys are successively affected by local disturbances in the circulation in the kidney, in the second all the cells are at once subjected to the same destructive agent. These facts can be interpreted only by recognizing a local cause for the spots of (parenchymatous) nephritis, and this spotty cause resides in the vascular changes. They are the cause of the nephritis and not the other way about.

It also becomes intelligible why little albumin, and few casts go with these types of chronic interstitial nephritis and why the output of water remains normal or, as some say, is even increased.

FIGURE 198.

There is plenty of healthy parenchyma left to secrete the normal amount of water and the spots of parenchyma affected path-

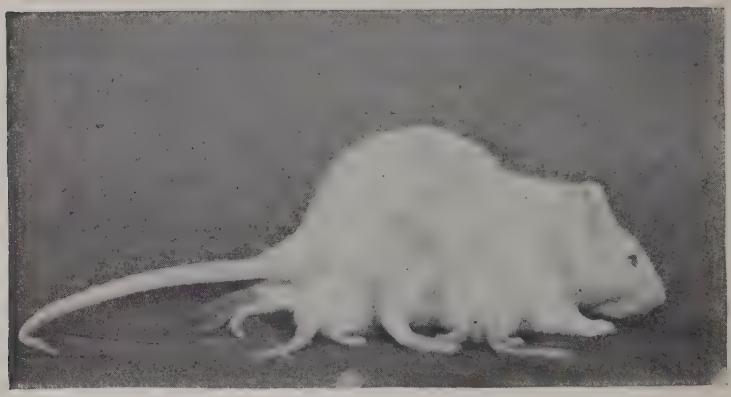


FIGURE 199

ologically give rise to but few casts and little albumin. Nor need the urine of such a nephritic be as highly acid as that of the frankly parenchymatous types, for it is the product of

that coming from healthy kidney mixed with that secreted by the nephritic spots.

§ 2

Just as the arteriosclerosis associated with kidney disease is not its consequence, but its cause, so the *hypertrophy of the heart* observed in such cases is not the consequence of the kidney, but of the blood vessel disease. This is clearly proved by the fact that the (physiologically) worst types of nephritis are those least liable to be associated with any hypertrophy of the heart. We do not find hypertrophied hearts in patients with a generalized parenchymatous nephritis, even though they may for years have suffered from this. Even gradual destruction of the kidneys is not followed by heart hypertrophy. I have under observation a man from whom one kidney was removed for infection eight years ago and who has had constantly since then large numbers of casts and much albumin in the urine from the remaining kidney. In spite of the evident destruction of much kidney substance he has no heart hypertrophy and a systolic blood pressure of 126 with a diastolic of 90 mm. of mercury. That, on the other hand, enormous hypertrophies of the heart may be associated with no kidney symptoms whatsoever is familiar to everyone.

In this subject of heart hypertrophy and chronic interstitial nephritis we seem, as clinicians, all too often to lose sight of the fact that the hypertrophy results in this case, as in any case, from the increased demand for work and the increased rate at which a given amount of work must be done. In the hypertrophy associated with arteriosclerosis these are determined by at least two changes in the circulation: the reduction in the caliber of the blood vessels and the loss of the elasticity of the blood vessel walls.

It should be clearly borne in mind that such roughening of the blood vessel walls as is observed has nothing to do with increasing the work of the heart. The friction encountered in driving the blood through the vessels is *not* that of blood against blood vessel wall, for since the blood "wets" the walls the friction is that of one layer of liquid over another.

With a given kind of blood, the blood vessels determine how much work and power is required to force the blood through them, only so far as their length (constant in body), diameter,

and elasticity are concerned. So far as the effect of changes in diameter is concerned (and in vascular disease the diameter of the blood vessels is diminished not only permanently because of vascular thickenings but also more or less intermittently by contraction (spasm) of the blood vessel coats), it must be borne in mind that the force required to drive a given volume of liquid through a tube increases about as the cube when the cross-section is diminished one-half. The loss of elasticity becomes a factor because, under physiological conditions, in the time of a single contraction of the ventricle an amount of blood, the equivalent of that ejected from the heart, is not at once pushed along the entire arterial and capillary bed out into the veins. Under normal circumstances it is simply thrown into the elastic arterial system, which dilates somewhat, and then, during the period that follows the systole of the heart, the elastic forces resident in the arteries slowly recoil and squeeze the blood out into the veins. When this elasticity is markedly diminished, the heart must in that proportion force its quota of blood during the time of each systole at once through the whole arterial and capillary system. In other words, the heart must do an amount of work in the time of the systole which it ordinarily does in the time of a systole plus a diastole plus the pause—roughly, say, in a third the time. To meet such a contract requires in engineering practice a three times larger engine, and the hypertrophied heart of the patient with sclerotic arteries represents the same idea put to work in nature.

A third factor tending to increase the demands upon the heart and so inducing its hypertrophy might reside in the blood itself. A liquid moves through a tube with greater and greater difficulty the more viscid it is. Anything that increases the viscosity of the blood, therefore, increases the amount of work demanded of the heart to push the blood forward. The viscosity of such colloid solutions as the blood is enormously increased by slight traces of acid [1] (P. von Schroeder,[2] W. B. Hardy [3] and especially Wolfgang Pauli and Hans Handovsky [4]) and so this factor which comes into play, not only in nephritis, but

[1] See page 145.

[2] P. von Schroeder: Zeitschr. f. physik. Chem., **45**, 106 (1903).

[3] W. B. Hardy: Jour. Physiol., **33**, 251 (1905); Proc. Royal Society, London, **79**, 413 (1907).

[4] Wo. Pauli and H. Handovsky: Biochem. Zeitschr., **18**, 340 (1909).

in hard work of any kind (laborers, athletes) needs to be considered. While certain clinical studies of blood viscosity have not yet brought proof that this undergoes any material change in nephritis, that such changes might well be expected is indicated by certain experiments of R. Burton-Opitz,[1] who found venous blood to have a higher viscosity than arterial, due to the carbonic acid in it, and the blood of dogs after the feeding of proteins (acid production) to have a higher viscosity than before such feeding.

§ 3

From what has been said it is clear that we cannot regard the heart hypertrophy as something primary, but as something secondary—as an example of the wide range of adaptation to changed conditions of which the cells and organs of our body are capable. Neither can we any longer consider the high blood pressure found in these cases and made possible through the fortunate possession of a larger and more effectively working pump as something bad. The high blood pressure is decidedly good, for *only through the increased pressure are the various tissues of the body guaranteed a blood supply sufficient to satisfy their physiological demands.* This holds for the kidney as for any other organ in the body. Only the increased blood pressure renders it possible that the normal parts remaining in an arteriosclerotic kidney maintain their normal activity. While conditions may exist or arise in the body which make the high blood pressure in itself dangerous (weakening of blood vessel walls and rupture), *a high blood pressure must with this exception not be regarded as something evil, but as an attempt on the part of the body to keep our various organs working at their physiological optimum.* Measures that *merely* reduce blood pressure can, therefore, hardly be looked upon with favor. *We must treat the underlying cause of the increased blood pressure, not the blood pressure itself.* To apply this to the kidney, with which we happen to be dealing, I can recall several cases of chronic interstitial nephritis with high blood pressure and cardiac hypertrophy in which a too enthusiastic desire to reduce the blood pressure led to the use of the nitrites, and with serious consequences. While the blood pressure fell, the urinary output also decreased, the albumin rose and casts

[1] R. Burton-Opitz: Pflüger's Arch., **119**, 359 (1907).

became numerous. In other words, the general fall in blood pressure made for a decreased circulation of blood through the kidney, and so for an aggravation of the kidney state. Only when we think that such a bad result will not follow the use of nitrites are we justified in using them. One case developed immediately after a single dose of amyl nitrite a complete anuria which some eight days later killed the patient.

2. On the Œdema of Nephritis

As far as I know, it is universally held that the œdema, often of extreme grade, so commonly found in nephritis is secondary to the kidney condition. We are especially prone to find a generalized œdema in the so-called parenchymatous types of nephritis. Œdema is not observed in the chronic interstitial nephritides associated with vascular disease except in the terminal stages. Why it occurs then will be discussed later. To avoid confusion we will temporarily limit ourselves to a discussion of the œdema so commonly observed in the frankly parenchymatous types. According to the prevailing notion, the œdema of the body generally is held to be secondary to the loss of kidney function. It is argued, in other words, that in an acute or chronic parenchymatous nephritis the kidneys are unable to excrete water properly and that this is, therefore, retained in the body with resulting œdema.

This view is also fundamentally wrong. If it were true that the œdema is secondary to the loss of kidney function, then we should be able, experimentally, to produce an œdema most rapidly by cutting the kidneys away. But when we take both kidneys out of an animal under light ether anesthesia, it recovers rapidly and continues to live for many days thereafter. In all this time it does not develop a particle of œdema, in fact, it steadily loses in weight. The one sign it shows is a progressive weakness, and finally it dies quietly.

Nature has performed this experiment many times in human beings, and what these show agrees absolutely with what is observed in the animals just described. Thus, after removal of an only kidney or after occlusion of both ureters by stone, or similar accidents which do away at once with the excretory function of the kidneys, the patient shows none of the signs of

a generalized œdema, nor, as we shall see later, any of the many other alleged consequences of loss of kidney function. Patients so affected have lived many days, and during this time have showed nothing but a progressive loss of weight and strength. James Taggart Priestley has reported the case of a man who lived thus for twenty-two days. There is only one way in which these constant and unequivocal results can be explained. *The œdema observed in nephritis is not secondary to the loss of kidney function. Kidney disease does not lead to the development of œdema.*

How then are we to interpret the combination of a generalized œdema with a nephritis? To do this correctly we need but consider the results of experiments in which poisons are injected into animals which are capable of producing what are generally considered the signs and symptoms of a parenchymatous nephritis. Uranium constitutes one of the accepted of this class. If rabbits or frogs are injected with small doses of a uranium salt they show very shortly thereafter the signs and symptoms of kidney involvement, as indicated by albumin, casts and blood in the urine with a diminution in the urinary output. They may be well marked at the end of twelve hours, and in one or two days may become so extreme that actual suppression results; but even if a fair amount of urinary secretion still persists the animals, nevertheless, begin to gain in weight. Thus, frogs show an increase in weight at the end of twelve hours, and at the end of twenty-four or forty-eight hours may have gained anywhere from twenty-five to forty or even fifty per cent in weight. At the same time they become sluggish in their movements, respond but slightly to stimulation and occasionally die in convulsions. In other words, the interference with kidney function may be slight as compared with nephrectomy, yet we see in the first days of these experiments degrees of œdema which are not encountered after total extirpation of the kidneys even if the animal or patient lives for weeks. Let us interject here that nephrectomized animals when injected with uranium develop an œdema as pronounced as that of animals with previously normal kidneys. How are these results to be explained?

The œdema of a parenchymatous nephritis is not secondary to the kidney disease, but represents in the involved tissues the same type of change as that which in the kidney we call nephritis. The swelling of the kidney represents the same process in this organ as

the swelling of the tissues of the body generally, and both of them are induced by the same cause. The intoxication which affected the kidney affected at the same time all the other tissues of the body and as it induced the swelling of the kidney with the other signs of nephritis, it also induced a swelling of the body tissues generally.

3. On the "Uremia" of Nephritis

The experiments and clinical observations discussed in the preceding paragraphs may be used to answer some questions associated with the problem of uremia. It is quite generally held that certain symptoms clinically considered characteristic of uremia, such as headache, vomiting, disturbances in vision, stupor, at times mania, disturbances in respiration, coma and death are secondary to loss of kidney function in the sense that a defective eliminatory power of the kidneys is supposed to lead to a retention of poisonous substances in the blood, to their accumulation in the brain, and so to the signs and symptoms just discussed. We will not deny that certain substances normally excreted through the urine may and do accumulate in the blood and so in the body tissues generally when for any reason the excretory function of the kidney is impaired. As is well known, however, none of these substances when injected into animals have thus far led to a reproduction of the picture which clinically goes by the name of uremia. As a matter of fact when the kidney function of an animal is done away with through double nephrectomy, or when such a condition is observed clinically through accident or the agencies of disease, the animal or patient shows none of the signs or symptoms generally considered uremic. As previously stated, both animals and patients suffer throughout their anuric period nothing but a progressive loss of strength, while consciousness, mental alertness, vision, etc., are maintained to the end. These facts are again interpretable in only one way: *What we call uremia clinically is not secondary to loss of kidney function.*

If now we try to say what the "uremia" of the clinicians is, then from a pathological point of view we have one solid fact upon which to build. Patients dead of it show anatomically an œdema of the brain. *The signs and symptoms which clinically are considered characteristic of uremia are the signs and symptoms of an œdema of the central nervous system.* The headaches, the

mania, the convulsions, the stupor and the coma are to be looked upon as signs and symptoms from a swollen brain; the blindness as symptomatic of an œdema of the optic nerve or retina; the vomiting, disturbed respiration and death as evidence of an œdema of the medulla. These œdemas of the central nervous system become therefore but part of that œdema which affects the rest of the body including the kidney, and underlying them all is the same cause.

The "uremia" observed in chronic interstitial nephritis associated with vascular disease is considered in the next paragraphs.

4. Reinterpretation of the Relation of Nephritis to the Clinical Manifestations Associated Therewith

With the above ideas in mind it is an easy matter to interpret correctly the clinical manifestations accompanying a nephritis, and without the self-contradictions which characterize our present points of view. The records of the obstetricians are filled with reports in which patients showing very slight or no urinary findings have nevertheless died in convulsions, while, on the other hand, every clinician has seen cases of complete abnormal urinary suppression without involvement of the central nervous system. On the old basis, according to which the symptoms from the side of the brain were consequent upon kidney disease, such findings could not be understood, but they are readily intelligible as soon as we recognize that the same poison which affects the one organ affects the other also. But a poison circulating in the body need not and does not affect all organs equally and to the same extent, wherefore it is easily understood that in a pregnancy intoxication we may at one time see the brain more involved than the kidney, while at another the kidney is more seriously affected than the brain. The same line of reasoning applies to the other organs of the patient, be they optic nerve,[1] medulla, or body tissues generally.

It is only because such organs as the brain, the optic nerve, the medulla and the kidney are hampered in their swelling by

[1] E. M. Baehr directed my attention to a football player who after each match game would go blind for twenty-four hours with an œdema of the optic nerve. As previously noted, an œdema of the kidney (as manifested by a decreased urinary output with albumin and casts) is the more obvious consequence of the acid intoxication following hard muscular work.

bony walls and tough capsules that they are most discussed. The liver, for example, is quite as commonly affected in a pregnancy intoxication as is the brain or kidney, but because its function is less obvious and because the capsule is more expansile so that a great degree of swelling is rendered possible without ultimately destructive effects, this question of liver involvement is not so much to the fore. Occasionally, however, the liver destruction is of sufficient grade to dominate the clinical picture, and then we hear of " altered liver metabolism," " yellow atrophy of the liver," etc. In any general intoxication such as that of pregnancy the liver is involved quite as commonly as the other organs of the body and is to be regarded as suffering from the same intoxication which is simultaneously attacking the other body structures.[1]

What we have illustrated here by a pregnancy intoxication holds for every general type of intoxication, as with chloroform, ether, alcohol, phosphorus, the various heavy metals, and the toxins of the infectious diseases. As we shall see later, the therapeutic methods which relieve the signs and symptoms referable to any one of these organs serve at the same time to relieve those referable to every other. Thus, alkalies, magnesium sulphate, or calomel, used to reduce the swelling of a liver, are likely to improve at the same time the headache, the nausea, the vomiting, and the œdema of the body generally, for the introduction of these substances into that colloid mass which we call the body tends to dehydrate all its organs simultaneously. The freed water reaching the kidney augments the urinary output.

We have now to interpret the extrarenal clinical manifestations observed in chronic interstitial nephritis. In the atrophic, secondarily contracted kidney there may, for reasons discussed above, be none at all. We see such extrarenal manifestations particularly in the chronic interstitial types found in association with vascular disease. Here again practically none of the ordinary signs and symptoms are to be considered secondary to the kidney condition. In the early stages of vascular disease all the signs and symptoms as observed in the different

[1] The dryness of the skin (lack of sweating) so frequently observed, especially in the infectious diseases, is to be similarly interpreted. The same poison which affects a kidney and interferes with the output of water by it (as in scarlet fever), affects the sweat glands similarly. The return of sweating, which the older doctors regarded so favorably, means in the skin what an increased urinary output means from the side of the kidney.

organs of the body are to be attributed primarily to an involvement of smaller or larger areas in the different organs of the body by the vascular disease. Any one organ, as the kidney, may escape entirely. We have already discussed the effects of progressive vascular disease as it affects the kidney. In the course of years one fragment after another suffers destruction with resulting atrophy. The remaining nubbin ("small red kidney") is, of course, subject to the same accidents which may affect a normal kidney, and so it is not impossible for it at any time to become the seat of a *generalized* parenchymatous nephritis. The "small red kidney" then becomes a "small gray kidney." This change is frequently noted in the terminal stages of blood vessel disease. Only rarely, however, does the involvement of the renal blood vessels themselves become so great as to lead to destruction of what remains of kidney substance. The reasons for such total destruction usually lie more definitely outside the kidney and may reside in intoxications similar to those which may affect any kidney. For the most part, however, it is dependent upon a failure of the circulation with its resultant lack of oxygen to all the tissues of the body, an abnormal production and accumulation of acid in them and a generalized œdema in which the kidney too is involved.

Others of the alleged consequences of chronic interstitial nephritis can also be intelligently understood as soon as the vascular disease is recognized as the primary source of the whole clinical picture. This is true, for example, of the hemorrhages into the retina and the disturbances in vision so often encountered. The "albuminuric retinitis" of the ophthalmologist is not the consequence of albuminuria or kidney disease, but merely an expression in the eye of the same changes which in the kidney give rise to nephritis. The swollen grayish patches or the hemorrhages in the eye are the consequence of vascular disease, as are the grayish spots and the hemorrhages found in the kidney. The ophthalmologist who discovers ocular changes should not make the diagnosis of nephritis, but one of vascular disease, which may presumably be affecting also the patient's kidneys. It should also be emphasized that the eye changes observed in conjunction with a frankly parenchymatous nephritis and those in a chronic interstitial nephritis of the type just discussed have a totally different significance. The visual

changes in the former represent in essence a toxic œdema of optic nerve or retina. In the former instance, if the pressure from swelling does not become too great or last too long, the blindness may therefore be expected to disappear. In the second case such complete recovery is largely impossible, for here the swelling, the degeneration and hemorrhage both by diapedesis and rupture are all too often expressions of irreversibly destructive lesions secondary to irremovable blood vessel disease. The distinction between the two conditions is analogous to that drawn between generalized parenchymatous and chronic interstitial nephritis in our previous discussion. While an œdema originally characterizes the involved portions in both instances, this is brought about in the one by a removable interference with the normal oxidative changes in the involved regions as induced by poisons, while in the other it is caused by a shutting off of oxygen through narrowed blood vessels which cannot be reopened.

When vascular changes affect the larger blood vessels going to the eye the entire globe may become the seat of an œdema. This marks the origin of the glaucoma so frequently observed in patients suffering with vascular disease, a problem which receives more detailed discussion later.[1]

How now are we to regard the headache, the vomiting, the mania, the coma and convulsions, the altered breathing and death, generally diagnosed as uremic, occurring in the course of chronic interstitial nephritis? We may observe these changes when the patient is suffering from no generalized œdema and when the output of water and dissolved substances by the kidneys is satisfactory. They are again not secondary to the kidney disease, but represent an œdema of the brain secondary to disease of the arteries supplying the brain and medulla. This is why a patient may show "uremic" attacks even though his kidney function is perfectly adequate. On the retention basis such an apparent inconsistency cannot be explained. The recurrent attacks of pulmonary œdema may also be interpreted in these vascular cases as local œdemas of the lungs secondary to vascular disease of the bronchial arteries.

It remains to discuss why attacks of "glaucoma," of "uremia," of pulmonary œdema, etc., are so often periodic in character

[1] See Part Seven, on Glaucoma.

instead of persisting after once being established. The reason for this resides in the fact that the factors conspiring to produce the localized œdemas do not always reside wholly in the blood vessels. An involved organ does not betray that it is suffering from vascular disease until this has advanced to a point where the organ approaches a state of partial oxygen want. In consequence of this, it begins to accumulate acids and similarly acting substances and to swell. Slight or no symptoms may attend this state, but when the products of hard work, of infection, of dietary indiscretion, of alcoholic excess or of a heart lesion are added, the involved organ swells more acutely and so gives rise to the obvious clinical manifestations with which we are familiar. If nature or we succeed in removing this added factor the patient may recover from his attack to get along until new indiscretions precipitate a second. The important difference between the "uremic" attack observed, for example, in an eclamptic woman and that observed in a man with vascular disease resides not in the attacks themselves or in the œdemas of the brain underlying both, but in the mechanism leading to these. In the former case recurrence is not to be anticipated after the pregnancy has been brought to a close, and the brain œdema has once been reduced, but in the second the persistent vascular disease continues to hold the patient liable to another attack.

As familiarly known, the sufferers from chronic interstitial nephritis do not show the generalized œdema, the decreased urinary output and the large numbers of casts with much albumin which distinguish the frankly parenchymatous form. In the terminal stages of the disease, however, this picture is frequently found. When it occurs our chronic interstitial nephritis has given way to a frankly parenchymatous form. Back of this change there must lie, as in the frankly parenchymatous forms, a general intoxication, and this intoxication, when not due to any of the accidents which may overcome the normal individual, is most commonly dependent on a failure of the circulation in consequence of a dilated heart, a failing heart muscle or defectively working sclerosed valves. The oxygen supply of the entire body of the patient is thereby diminished, and, as this occurs, all his organs begin to develop an œdema. It is for this reason that his body tissues generally swell, his liver now shows enlargement

and the symptoms of a brain œdema gradually supervene. At the same time the urinary secretion falls, the casts increase and the albumin content rises. In this stage the blood pressure may also show signs of falling—a sign alike of the failing cardiac efficiency and oncoming death of the individual and a conclusive argument against the notion that the high blood pressure was in itself either bad for the patient or responsible for his condition.

5. Remarks on the Etiology of Vascular Disease

When we make certain types of nephritis secondary to vascular disease and the alleged consequences of such nephritides but the expression of vascular disease in other organs, it becomes apparent that a rational therapy for the whole can hope to rear itself only upon what we assume to be the causes of the blood vessel changes. As such causes almost everything has been listed, but it is certain that many or most of these alleged etiological factors have nothing to do with the *production* of the disease. However injurious may be the effects of alcohol, coffee, tobacco, hard work, intestinal fermentation, the products of an infectious disease, etc., upon a man with an established vascular disease, they have, as a matter of fact, nothing to do with its origin. Not only has everyone seen individuals who for years have been addicted to the abuse of alcohol or have worked excessively, or have been the subjects of steady intoxication, and who, nevertheless, show no particle of vascular degeneration, but simple study of the lesions characteristic of vascular disease is sufficient to indicate that no generalized intoxication can lie behind the process. The lesions of blood vessel disease are focal in nature, and even when the involved spots become so numerous that large portions of the blood vessels are involved, goodly portions of healthy blood vessels are, nevertheless, always to be discovered in even the most advancedly degenerated cases. *Such lesions cannot be explained on the basis of a general poisoning.* Alcohol, the products of hard work, the toxins of an infection, a soluble metallic salt or any other soluble poison cannot course through the blood vessels and pick out only limited areas. Such poisons would involve the whole of the media or the whole of the intima of the blood vessels, and at once. *To get the spotty lesions characteristic of*

vascular disease we must have a spotty cause. A generalized intoxication does not constitute such.

Through the brilliant clinical studies of FRANK BILLINGS [1] and the bacteriological researches of EDWARD C. ROSENOW [2] we have obtained light regarding the origin of such spotty lesions. ROSENOW has showed that the lesions of endocarditis, of pericarditis, of articular and muscular rheumatism, of certain types of gastric ulcer, cholecystitis, appendicitis, and nephritis are in essence all the same. Micro-organisms are responsible for these pathological entities, producing their initial lesions by collecting in clumps in the tiny blood vessels supplying the heart valves, the pericardium, the joint surfaces, the tendinous insertions of muscles, the gastric mucosa and the kidney. The injury to the blood vessels by such bacterial emboli is followed by a thickening of the intima and thrombotic changes, the sum total of which leads to anemia and œdema of the involved part, to be followed all too often by degeneration and destruction.

The anatomical lesions characteristic of vascular disease are identical with those observed by ROSENOW *in other diseases and must have behind them an infectious organism.* When vascular disease attacks the larger blood vessels the original lesions occur in the media. The series of changes (intimal thickening, swelling, degeneration) observed here are really consequent upon changes involving the vasavasorum, and these changes in the vasa-vasorum are identical with similar changes which may be observed in any of the smallest blood vessels found elsewhere in the body. The primary changes of vascular disease are similar in nature to those produced anywhere else in the body when small blood vessels become the seat of infectious embolism. The etiological importance of the spirochete of syphilis in the production of blood vessel disease has long been recognized. What we need to make further progress toward a correct understanding of its nature and cause is more bacteriological study and less profitless chasing of "metabolic" will-o'-the-wisps.

There are already at hand many suggestive studies which indicate the parasitic origin of the initial lesion of vascular

[1] FRANK BILLINGS: Arch. Int. Med., **4**, 409 (1909); **9**, 484, (1912); Jour. Am. Med. Assoc., **71**, 819 (1913); **63**, 11 (1914).

[2] EDWARD C. ROSENOW: See page 815, as well as his various papers of the last five years in the Journal of Infectious Diseases and the Journal of the American Medical Association.

disease. Y. Manouélin [1] found that the repeated intravenous injection of yellow and white staphylococci killed at 56°, 60° and 100° C. into rabbits and monkeys for six to nine months resulted in the production of atheroma in 84 per cent of rabbits and in five out of six monkeys; while T. B. Hartzell and A. T. Henrici[2] describe incidentally the observation of vascular changes after the intravenous injection of streptococci isolated from alveolar abscesses. Even when due allowance is made for the "spontaneous" vascular lesions observable in various laboratory animals these findings are nevertheless striking. James J. Hogan [3] has moreover isolated organisms of the streptococcus group from the walls of varicose veins removed surgically while E. R. Le Count and Lelia Jackson [4] describe the localization of organisms of the streptococcus group in the small arteries of the kidney—the very spots in which vascular disease first involves the kidney to produce the beginnings of chronic Bright's disease.

To accept the infectious nature of vascular disease is to stimulate a therapeusis which, it seems to me, promises more for the patient than the old expectant scheme of treatment. To connect vascular disease with a syphilitic infection is to get a rational basis for the use of iodids, mercury and other antisyphilitic agencies. Where a syphilitic infection can be eliminated, attention to infected tonsils, infected teeth, infected ears, old genito-urinary and pelvic infections, etc., has, in my opinion, yielded better results than our former empirical methods.

IX

THE DISTURBANCES IN SECRETION IN NEPHRITIS

1. General Considerations

The changes observed in the secretion of urine in any case of nephritis fall into two groups: the changes in the amount secreted in any unit of time and the changes in the quantitative composition of the urine. In all except certain of the so-called chronic

[1] Y. Manouélin: Ann. l'Inst. Pasteur, **27**, 12 (1912).

[2] T. B. Hartzell and A. T. Henrici: Jour. Am. Med. Assoc., **64**, 1055 (1915).

[3] James J. Hogan: Personal communication (1913).

[4] E. R. Le Count and Lelia Jackson: Jour. Infectious Dis., **15**, 389 (1914).

interstitial types of nephritis the secretion of water is diminished. In the chronic interstitial types associated with blood vessel disease it is said to be increased. So far as the secretion of dissolved substances in nephritis is concerned, it is generally accepted that (diet duly considered!) there exists not only a diminution in the total amount of dissolved substances eliminated, but variations in the proportion of the dissolved substances when compared with other and regarded in the light of the way in which these same substances are eliminated during health. What happens here is interesting. We find that certain substances may be eliminated as well by the diseased kidney as by the normal. Certain other substances are eliminated in much smaller amounts than is normal, so small, in fact, that it is often said not at all. Experiments and observations to indicate that a nephritic kidney may secrete yet other substances even *better* than a normal kidney are not on record so far as I know. Quantity of urine duly considered, such a thing is theoretically not impossible.[1]

It is generally said that in chronic interstitial nephritis associated with vascular disease the secretion of water by the patient is not diminished as in the parenchymatous forms, but is normal in amount, or, as the majority of clinicians and pathologists are wont to say, is increased in amount.

To the claim that the urinary output is increased, serious objection must be made. It is better simply to say that the output is normal. Urinary secretion is normal if (with due regard to loss of water through skin, lungs, and intestinal tract) all the water consumed by an individual is excreted again, as urine—that is to say, none is retained (œdema) and not more than has been consumed is excreted (abnormal loss). If a man consumes only a liter of water a day and secretes a liter of urine (skin, etc., being ignored) his urinary secretion is normal, and if he consumes twenty liters and secretes twenty it is normal. We may differ as to which of these amounts, if either, we consider as normal (better optimal) from the standpoint of *consumption*, but so far as secretion is concerned, both are normal. And for

[1] Since this was first written Walter A. Baetjer (Arch. Int. Medicine, **11**, 593 (1913)), has proved that the nephritic kidney secretes certain substances better than the normal, and has collected illustrations from the older literature which support his own findings.

this reason I would insist that the patient with chronic interstitial nephritis who happens to consume in response to his tastes three liters of water and so secretes three liters of urine (skin, etc., again ignored) has not an increased urinary output, but a normal one.

The amount of water consumed by an individual is governed by his sense of thirst, which represents in essence a certain degree of dryness of some or all of his tissues. Such a dryness tends to be increased in a patient with vascular disease. While it is true that certain regions in his various organs are through the blood vessel disease rendered liable to œdema, the blood vessel disease does not affect all the vessels to the same extent and so, because of the increased blood pressure, etc., such unaffected regions may actually be better supplied with blood than normally. They therefore tend to be drier, or in the case of the kidney, such non-involved regions would actually secrete water better than normally. Hence a tendency to an even better than normal water elimination, a greater dryness of the tissues generally, a greater thirst, and a greater water consumption.

The reasons for the normal water output by the patient with chronic interstitial nephritis associated with vascular disease reside in the fact that he still has large amounts of kidney substance acting normally, and as a quarter of his total kidney substance easily suffices to yield a normal water output, he shows no decrease in this as long as such an amount remains available. The nephritic portions of the kidney do not secrete water in chronic interstitial nephritis any more than do the cells in the generalized parenchymatous case. *It is the uninjured cells between the nephritic portions which keep the water output in a case of chronic interstitial nephritis up to normal.* When for any reason enough or all of the remaining portions of still functioning kidney in chronic interstitial nephritis become involved, then the urinary secretion falls. The claim that water secretion is normal (or increased) in chronic interstitial nephritis holds only as long as sufficient quantities of normal parenchyma remain between the involved areas.

2. The Secretion of Water by the Nephritic Kidney

In support of the thesis that an abnormal accumulation or production of acid in the kidney constitutes the basic cause

of every nephritis, it would be sufficient in this section merely to show that such a condition always leads to a decrease in the secretion of water by the kidney. We shall, however, not stop with this but try to indicate in a little more detail where lies the point of attack for the acid that is responsible for such a change in secretion.

It is an easy matter to show that *the direct introduction of acid into the kidney, or any method capable of leading to an abnormal acid content in the kidney, is followed by a decrease in urinary secretion which may go to the point of absolute stoppage.* This is clearly evident in the accompanying drawings, which have been constructed from the experiments detailed in various divisions of this volume.

Fig. 201 on page 653 has been introduced to show the *normal* secretion of urine in three rabbits, kept on a mixed diet, when these are brought into the laboratory and are *loosely* tied into an animal holder. When the animals are *snugly* tied into a holder, the urinary secretion is decreased in amount. This is clear from Fig. 202 in which are shown the curves for the urinary secretions obtained in the animals that were rendered albuminuric by this means (Experiments 84, 85, 86 and 87). If instead of such a general state of lack of oxygen in the body we interfere locally with the blood supply to the kidney, as through clamping of the renal blood vessels, the same great fall in urinary output is observed, as is evidenced in the lowermost curve of Fig. 207. But to show that it is really the acid developed in the body as a whole, or in the kidney specifically, that under these circumstances is responsible for such a fall in secretion, it is best to inject the acid directly. The effect of such a proceeding is shown in Fig. 205 based on Experiments 59, 60 and 61. It would be purposeless to multiply these experiments to support further the contention that an abnormal acid content in the kidney leads to a decrease in the secretion of water. As a matter of fact it finds daily corroboration in the decreased urinary output observed in all those clinical cases, such as heart disease, respiratory disease, etc., which we know to be associated with an abnormal accumulation and production of acids in the body.

But how may we imagine the acid to be effective in this regard? A proper answer to this question demands a critical review

of all the various theories that have been proposed from time to time to explain the mechanism of normal urinary secretion, and this would lead us too far afield.[1] We can, however, help toward a more circumscribed formulation of the whole problem.

Defined physicochemically, the problem of water secretion by the kidney is essentially the problem of how water contained in the blood is made to pass through a solid (hydrophilic) colloid membrane, this being represented, in the case of the kidney, by the various cells and their intercellular substances that lie between the blood on the one hand and the urine on the other.

In the light of what has been written in the preceding pages and accepting as best supported the theory that water is lost from the kidney by a process of filtration, the action of an acid or similarly acting substance in inhibiting or suppressing the secretion of water may be conceived of somewhat as follows:

(1) The acid acts upon all the tissues of the body including the blood and lymph. The increased hydration capacity resulting from this makes these tissues hold more water in combined form (maintenance of body œdema) while at the same time it prevents water becoming "free" in the arterial blood stream. A first reason for non-secretion of urine is therefore resident in the fact that the blood passing through the kidney contains no "free" water.

(2) A second action of the acid is upon the colloids of the kidney themselves. The consequence of this is again swelling of the kidney substance or, in the terms of secretion, a swelling of the filtration membrane through which "free" water alone can pass under normal circumstances. Such swelling closes the pores of the filter so that even when "free" water is brought to the kidney it cannot be given passage. The process is, in other words, analogous to failure of the hydrophilic colloid membranes (like sodium stearate) to give passage to water under a given hydrostatic pressure whenever the porosity of such a colloid membrane is reduced.

3. The Secretion of Dissolved Substances by the Nephritic Kidney

As already noted, the nephritic kidney shows deviations from the normal secretion of dissolved substances by it in two directions. Other conditions remaining the same there is, first,

[1] See the previous sections on urinary secretion beginning on page 325.

a decrease in the absolute amounts of the various substances secreted, and second, a change in the relative proportions that these bear to each other when compared with the secretion of these same substances as observed in health. The nephritic kidney secretes some substances as well as does the healthy kidney, others decidedly less well, *a third group even better.*[1] It is our problem to say how such a condition as an acid production in the kidney brings this state of affairs to pass. In order to do this we must recall some of the facts of normal secretion by the kidney.

As is familiar to everyone, a secretion of some substances proportionately more easily than others, in other words, a "selective" secretion by the kidney, is not characteristic of the diseased kidney, but of the healthy kidney as well. This is really the rock on which most of the mechanical, or to use a broader and better term, non-vitalistic or physico-chemical conceptions of urinary secretion have foundered—and these founderings have given momentary comfort to those who believe that kidney secretion, as many another physiological phenomenon, is "vital" in character. But such a pessimism would seem to be premature, for we are already familiar in physical chemistry with not a few systems in which differences in the concentration of any substance are easily maintained over indefinitely long periods of time, and, of course, without the assistance of those "peculiar" forces believed by some to inhabit the living cell. Reference is here made to *the difference in the distribution of any substance between two phases* (*the distribution coefficient.*[2]

Through the work of Hans Meyer and E. Overton the differences in the solubility of such substances as alcohol, ether, chloroform, morphin, cocain, etc., in water and in fats and fatlike bodies (lipoids)—their distribution coefficients between two solvents—have been shown to explain very satisfactorily why these substances not only diffuse with greater speed into and through cells, especially rich in the fatlike bodies (the fat cells and the cells of the central nervous system), than into and through such as contain these in smaller amounts (yellow elastic tissue, white fibrous tissue), but why in the end they are found in larger absolute amounts in some tissues than in others.

[1] See W. A. Baetjer: Arch. Int. Med., **11**, 593 (1913).

[2] See page 207.

A second property of protoplasm which permits one cell or tissue to take up more of any given substance, and this more speedily than is the case with another cell, is the character of the colloids contained in the cells and their state. This is one of the reasons why certain stains when injected intravenously are not taken up with the same speed, or to the same extent, by all the tissues of the body.

A third property of protoplasm, which makes for inequalities in the distribution of a substance, resides in the chemical differences existing between different kinds of protoplasm. Certain, but by no means all, of the "vital" and "specific" protoplasmic stains are examples of this class. In these a chemical combination results between the dye and the chemical compounds found in some cells.

What use can we make of these facts in the explanation of the alterations observed in the secretion of dissolved substances by the nephritic kidney? In discussing the colloid-chemical theory of urinary secretion,[1] I tried to show how the "selective" character of secretion may be explained in the following way:

All secretion of dissolved material by the kidney is dependent upon a primary secretion of water by the kidney. After the water is secreted all the constituents which characterize it as urine come to be added to it, in its course through the uriniferous tubules, by a process of leaching out of the dissolved substances present in the kidney cells. But in this process of leaching out, not all the constituents present in the protoplasm leave the cells in which they are originally present with the same ease. Depending upon the character of the dissolved substance, and the state of the protoplasm as to lipoid content, colloid state, and chemical composition, the water present in the uriniferous tubule may come to take up the dissolved substance to an extent which allows it ultimately to be found here in a lower concentration than in the kidney cells, in the same concentration, or in a greater one. It is all a matter of equilibrium. But the equilibrium points with different substances are different, and so the relative amounts of these different substances that appear in the urine are also different. In other words, the (normal) leaching out is "selective," or, to put it biologically, the "secretion" of the dissolved substances is selective.

But this leaching out of dissolved substances from the kidney

[1] See page 367.

is only one-half of the process of urinary secretion. The other half is the process of the absorption of dissolved substances from the blood by the kidney cells preparatory to their secretion into the lumen of the uriniferous tubules. This is also a selective process, and here the same laws of lipoid solubility, colloid adsorption, and chemical combination, which have already been discussed in the leaching out process, again come into play.

All these various processes of absorption and secretion of dissolved substances by the kidney cells are most markedly influenced by the content of acid, of salts, etc., in them, and it is for this reason that the observed variations from the normal in the secretion of dissolved substances by the nephritic kidney occur.

It is easily appreciated why there must be a decrease in the *absolute amount* of dissolved substance secreted by the nephritic kidney. If the secretion of water is diminished, then not as much dissolved substance can be leached out of the kidney parenchyma as when more is secreted. Into this, however, enters the element of *time*. When much water is being secreted by a kidney its discharge into the pelvis of the kidney is also hastened. The time that a given portion of the urine (secreted as water initially) is in contact with the kidney cells is thereby diminished, and so not all that this water is *capable* of absorbing is taken up. When the water is secreted more slowly, the ultimate equilibrium point for the distribution of dissolved substances between the kidney and the urine is more nearly approximated. We find daily expression of this in the clinical observation that after the consumption of much water the concentration of the urine falls, while with a diminished intake of water, or when the kidney cannot secrete it (as in nephritis), the concentration of the urine becomes progressively higher. Yet, other things being equal, the absolute amount of any dissolved substance secreted by the kidney must be the greater, the larger the absolute amount of water secreted by the kidney in any unit of time.

To illustrate how the increased acid content in the kidney in nephritis leads to variations in the secretion of the dissolved substances, I introduce some simple test-tube experiments and experiments on rabbits, which concern themselves particularly with that part of the selective secretion which deals with the state of the colloids in the kidney cells. This constitutes by far the most important part of the whole problem of selective absorption and secretion, for the state of a colloid in the body

is more easily affected by external conditions than is the solvent property of a lipoid, or the chemical character of any part of living protoplasm. As the various dyes betray themselves not only qualitatively, but, in a sense, also quantitatively, to the naked eye, illustrations of the "absorption" and the "secretion" of these, under conditions that interest us in our discussion of nephritis, seemed to me best suited to our needs. I chose, moreover, dyes that have been used physiologically in the study of the kidney. The results of a few experiments on the staining of fibrin, which are familiar to any worker who has at all touched upon the problem of dyeing, and which might be multiplied indefinitely by using other dyes and different colloids, are shown in Fig. 200.

Tube 1 contains an aqueous solution of toluidin blue. If into another tube (2), containing the dye in the same concentration, some powdered fibrin is dropped, this soon absorbs most of the dye and stains intensely blue. The supernatant liquid retains only a faint tinge of the blue, but this remains indefinitely. If the supernatant solution is carefully pipetted off, and distilled water is placed over the dyed fibrin, the water now slowly turns blue. In this way, through successive washings, we can again get considerable of the blue out of the fibrin. In other words, the fibrin absorbs the dye until an equilibrium is reached between the concentration of the dye in the fibrin and the concentration of the dye dissolved in the supernatant liquid. If we disturb this equilibrium by removing the blue solution above the fibrin and substituting water for it, some of the dye comes out of the fibrin until equilibrium is once more established.

If we will now substitute the words kidney colloids for fibrin we have what happens in the kidney when it secretes any dye. The absorption of the dye by it from the blood is analogous to the first series of changes, the leaching out of the dye by the urine to the second. We see also why the quantity of urine secreted and the time that this remains in contact with the kidney cells are of such importance. This corresponds with the renewal of the distilled water above the dyed fibrin and the time this is allowed to remain there before being pipetted off.

What happens if we introduce into this whole system a trace of acid? The result is shown in tube 3. The fibrin swells somewhat, but the toluidin blue is now scarcely taken up. The

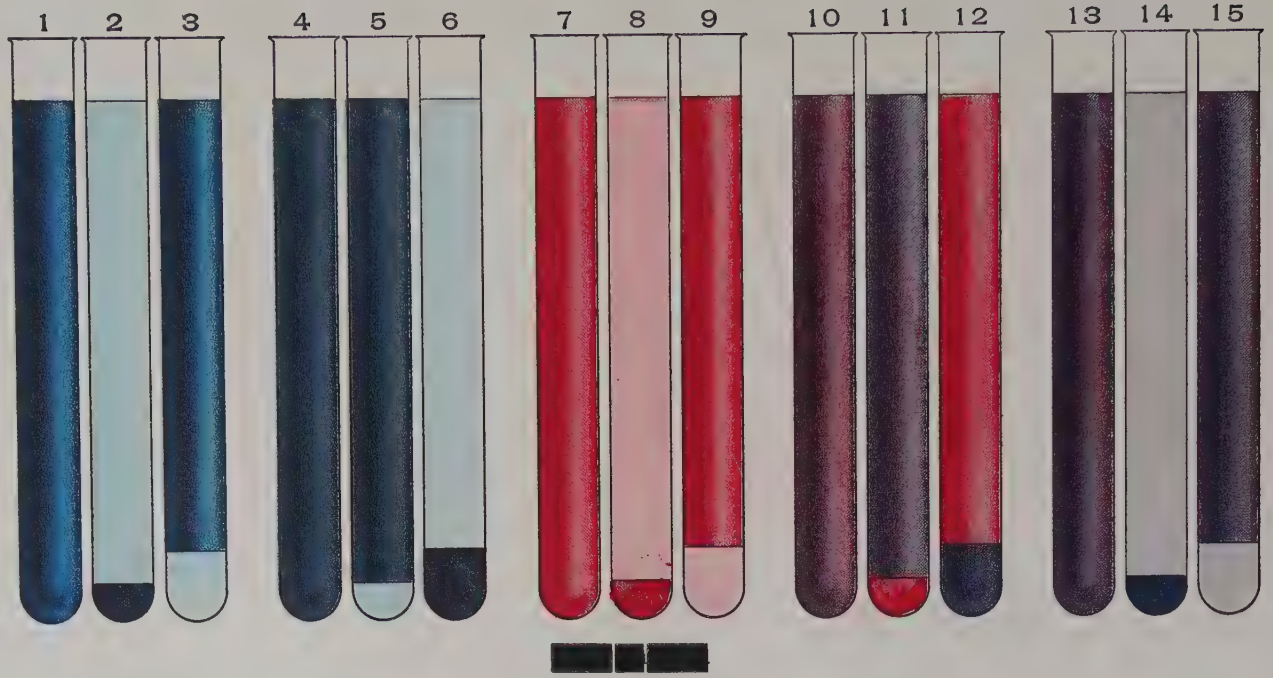


FIGURE 200.

supernatant liquid remains practically as blue as the control tube 1. What would this mean when applied to the kidney affected with nephritis, for which we have maintained that an abnormal acid content is responsible? That the kidney would swell as does the fibrin, we already know. But such a kidney would now not absorb the toluidin blue preparatory for secretion as does the healthy kidney. Yet, we must not hastily conclude herefrom that under such circumstances the kidney would necessarily secrete this dye badly. Once any dye was in the kidney colloids it would rapidly diffuse into the urine, not only because the kidney colloids are not holding on to the dye particularly firmly, but because the acid liable to be in such urine as is secreted from the nephritic kidney would further favor the passage of the dye into it.

In tubes 4, 5, and 6 are shown a parallel series of experiments carried out with sodium indigosulphonate. It is clear that with this dye conditions are exactly the reverse of those obtaining in the case of toluidin blue. The very circumstances which favor absorption before, hinder it here, and those which hindered it before now favor it. In tubes 7, 8, and 9 are shown the results obtainable with neutral red, which, it will be observed, behaves like toluidin blue.

But the kidney is not thus offered one substance at a time to secrete into the urine. The blood that passes through this organ brings it many at once. What must be the behavior of the tissue colloids under such circumstances? As tubes 10, 11, and 12, and tubes 13, 14, and 15 clearly show, a colloid under such circumstances behaves toward each of the substances offered it as though the others were not present. In tube 10 is shown the effect of mixing sodium indigosulphonate and neutral red. If some fibrin is introduced into this mixture it absorbs the red (chiefly) and leaves behind (almost) all the blue. This would correspond with the kidney function in health. If now an abnormal amount of acid were present in the kidney (nephritis) just the reverse would result—the red would now be left behind in the blood, while the blue would be absorbed.

In tubes 13, 14, and 15 are shown the results on the staining of fibrin when toluidin blue and neutral red are mixed. The resulting color is shown in tube 13. In the presence of fibrin alone both of the dyes are absorbed as shown in tube 14, but if a little acid is present, or is subsequently added, the fibrin

fails to stain. Fig. 200 was painted from the results obtained in Experiment 83, after the tubes had stood some eighteen hours. Marked differences in the degree of staining are readily visible, however, after ten minutes.

EXPERIMENT 83.

1. 15 cc. .01% toluidin blue+15 cc. water.
2. 15 cc. .01% toluidin blue+15 cc. water+0.4 gram fibrin.
3. 15 cc. .01% toluidin blue+15 cc. n/20 acetic acid+0.4 gram fibrin.
4. 15 cc. .02% sodium indigosulphonate+15 cc. water.
5. 15 cc. .02% sodium indigosulphonate+15 cc. water+0.4 gram fibrin.
6. 15 cc. .02% sodium indigosulphonate+15 cc. n/20 acetic acid+0.4 gram fibrin.
7. 15 cc. .02% neutral red+15 cc. water.
8. 15 cc. .02% neutral red+15 cc. water+0.4 gram fibrin.
9. 15 cc. .02% neutral red+15 cc. n/20 acetic acid+0.4 gram fibrin.
10. 15 cc. .02% sodium indigosulphonate+15 cc. .02% neutral red.
11. 15 cc. .02% sodium indigosulphonate+15 cc. .02% neutral red +0.4 gram fibrin.
12. 7½ cc. .04% sodium indigosulphonate+7½ cc. .04% neutral red +15 cc. n/20 acetic acid+0.4 gram fibrin.
13. 15 cc. .01% toluidin blue+15 cc. .02% neutral red.
14. 15 cc. .01% toluidin blue+15 cc. .02% neutral red+0.4 gram fibrin.
15. 7½ cc. .02% toluidin blue+7½ cc. .04% neutral red+15 cc. n/20 acetic acid+0.4 gram fibrin.

The details of this experiment have already been discussed in the text.

It follows from all this that the presence of a little acid in such colloid material as composes the kidney must be followed by profound changes in the character of the secretion of dissolved substances by it as compared with the normal secretion of these same substances. But depending upon the way in which the acid displaces the equilibrium point, it is clear that, with otherwise constant conditions, the secretion of any substance may not only be decreased or simply remain unaffected, but it may actually be increased.

Before closing this chapter it is well to refer to a few animal experiments which show that what has been said above regarding the staining of fibrin actually holds in the case of the living animal. As pointed out in our discussion of the experiments of HEIDENHAIN, DRESER, and NUSSBAUM, these authors found

the kidneys of their experimental animals stained most deeply, and most generally, with sodium indigosulphonate or acid fuchsin (which stains fibrin just as does sodium indigosulphonate) when conditions favoring the accumulation of acid in the kidney were most clearly at hand. This corresponds with the improved tendency of fibrin to stain with these dyes when an acid is present. When in a rabbit under morphin anesthesia the artery to one kidney is clamped for an hour or two, and the clamp is then removed while sodium indigosulphonate or acid fuchsin is injected intravenously, it is found that *the clamped kidney not only stains sooner than the unclamped one, but more intensely.* When frozen sections are made of the two kidneys the dye in the healthy kidney is found only in the lumina of the uriniferous tubules, while in the ligated one it is found in the cells themselves. And yet a kidney so clamped for an hour or two may not yield any urine for hours afterwards. *Mere staining of the kidney, as already noted above, can not at once be taken as an index of secretion.*

The reverse of this experiment can be done with neutral red. Here the normal kidney stains well and rapidly, while *the clamped one remains without color,* owing to the acid developed in it in the absence of a circulation.

After what has been said it must be self-evident that so many factors enter into the picture of the secretion of any dissolved substance by the kidney—so many at which we can to-day but guess in a clinical case—that conclusions regarding the functional activity of the kidney, as derived from a study of the elimination of some one compound swallowed by or injected into the patient and sought for in his urine, must only be drawn with the greatest care. Even though we ignore all other elements of error, the state of the blood, the state of the kidney colloids, and the state of the urine all influence the rapidity and perfection of the elimination of the substance in so marked and (for us) uncontrollable a way, that trustworthy conclusions are hardly possible, and when we take the liberty, as is so often done, of applying without modification what we may have learned from the elimination of one substance to some other or all other constituents found in the urine, then we are on dangerous ground indeed. Until we have learned far more regarding the laws that govern the secretion of dissolved substances by the kidney than we know to-day, *we had best*

accept as the most reliable test for the functional activity of this organ its ability to eliminate water.[1]

X

SOME EXPERIMENTAL FOUNDATIONS FOR THE TREATMENT OF NEPHRITIS. FALLACY OF SALT RESTRICTION IN NEPHRITIS AND ŒDEMA

1. Introduction

Before use is made in clinical practice of the rather obvious conclusions to which the considerations of the previous pages compel us, conservatism demands that we apply a further test to them. We have labored thus far to show how a parallelism exists between the changes that various protein colloids undergo in the presence of acid and similarly acting substances, and the changes that are observed in the kidney when this becomes the seat of a nephritis. We have noted how the swelling of the kidney in nephritis is like the swelling of fibrin or gelatin in water when a little acid is added to this; how under the same circumstances some of the colloids go into solution, and so the development of an albuminuria is simulated; how when a colloid of the nature of casein is mixed with these, it is precipitated under conditions which make the others swell, thus behaving like certain granules observed to arise in the cells of the kidney under conditions associated with a nephritis.

In studying the behavior of the pure colloids we learned more than this. We learned that the swelling of the colloids could be reduced, not only by neutralizing the acid, but by adding to the acid any neutral salt. So far as the precipitation of casein was concerned the salts divided themselves into two groups—the one added itself to the effect of the acid and favored precipitation, the other counteracted such an effect. If now our contention is correct that the series of changes observed in these simple colloids and in the kidney are identical in character, then it is to be expected that the *administration of properly selected salts should relieve the various signs characteristic of a nephritis.*

[1] See page 757.

That such is the case is not only a long accepted clinical fact, but can easily be proved experimentally.

Of the many salts which might be tested one can, of course, foresee that those will give best results which have no " specific " poisonous action, which have the power of neutralizing acid, and which combine a maximum of those effects which tend on the whole to help the nephritis (reduction of protein solubility and swelling of the kidney) with a minimum of those which aggravate such a condition (augmentation of protein precipitation in the cells). But neutral salts are also effective in reducing the solution and the swelling of such colloids as fibrin, gelatin and serum albumin. Of the long list of such, one has in recent years been particularly signaled out for attack. It has been widely taught that sodium chlorid is not only not good for a nephritic, but distinctly bad, in that it is held to increase not only the signs of a nephritis, but is supposed to be responsible for a retention of water and so for the aggravation of the œdemas so often seen accompanying such. Neither in the observations on pure proteins nor in the experiments on urinary secretion can a single fact be found to support such a view. As the following experiments show, *various neutral salts decrease the signs and symptoms of nephritis, and sodium chlorid is no exception to this rule.*

In order to show that salts inhibit the development of the signs of a nephritis, it was first necessary to decide upon satisfactory methods of producing a nephritis experimentally in animals, upon which might then be tried the action of various salts. Three different ones were employed: interference with the respiration of the animal, the intravenous injection of acid, and direct clamping of the renal blood vessels. Of all these the last named is probably grossest in its effects upon the kidney. For the sake of comparison the protocols of the experiments on the animals which served as controls have been inserted in each case.

2. Asphyxial Nephritis

Let us first consider the nephritis that develops in rabbits, when these are tied into the animal holder sufficiently tightly to interfere with their respiration. One always gets an albuminuria after such a procedure, as Experiments, 84, 85, 86 and 87 show.

EXPERIMENT 84.—White rabbit; weight 898 grams. Fed wheat and grass. *Snugly* tied into holder. Urine obtained with soft rubber catheter.

Time.	Urine in cc.	Remarks.
3.00	.....	Bound into holder.
3.30	3.7	Alkaline to litmus paper. No albumin.
3.45	5.0	Clearer urine. Neutral to litmus paper. Trace of *albumin*.
4.00	3.0	Clear urine. Neutral to litmus. *Albumin* present.
4.15	1.8	Clear. Neutral to litmus. *Albumin* present in every sample, and increasing in amount.
4.30	0.9	
4.45	1.1	
5.00	1.5	
5.15	1.8	
5.16	.....	Animal seems entirely well. Returned to hutch.

EXPERIMENT 85.—Belgian hare; weight 1226 grams. Fed wheat and grass. *Snugly* tied into holder. Urine obtained with a soft rubber catheter.

Time.	Urine in cc.	Remarks.
2.45	Few drops	Alkaline, thick, chrome yellow. No albumin.
3.00	1.0	
3.15	0.5	
3.30	Few drops	
3.45	Few drops	Neutral and clearer. Trace of *albumin*.
4.00	Few drops	Neutral and clearer. *Albumin* present in every sample.
4.15	Few drops	
4.45	2.0	
5.00	Few drops	
5.15	Few drops	
5.16	.....	Animal released and returned to hutch.

EXPERIMENT 86.—Belgian hare; weight 1020 grams. Fed wheat and grass. *Snugly* tied into animal holder. Urine obtained with a soft rubber catheter.

Time.	Urine in cc.	Remarks.
3.30	3.0	Tied down. Turbid, dark yellow. Alkaline to litmus. No albumin.
3.45	0.7	
4.00	0.5	
4.15	Few drops	
4.30	2.4	Turbid, dark yellow, alkaline to litmus. No albumin.
4.45	8.5	Clearer, pale yellow. Acid to phenolphthalein. *Albumin* present.
5.00	4.0	Clear, acid to phenolphthalein. *Albumin* present in every sample.
5.15	2.0	
5.30	Few drops	
5.45	Few drops	
6.00	3.0	

EXPERIMENT 87.—Belgian hare; weight 1100 grams. Fed wheat and grass. *Snugly* tied into holder. Urine obtained with a soft rubber catheter.

Time.	Urine in cc.	Remarks.
4.00	1.0	
4.15	2.0	
4.30	Few drops	Tied down. Alkaline, turbid, thick. No albumin.
4.45	1.5	
5.00	2.0	
5.15	1.5	
5.30	2.5	Urine clear, acid to litmus. *Albumin* present in every sample.
5.45	3.0	
5.46	.....	Liberated. Returned to cage.

When, now, rabbits are treated from an experimental standpoint in an identical way but have a concentrated salt solution injected intravenously, *the albuminuria does not develop*. This is shown by Experiments 88 and 89.

EXPERIMENT 88.—Black rabbit; weight 917 grams. Fed wheat and grass. *Snugly* tied into animal holder. Urine obtained with a soft rubber catheter. 105 cc. m/2 (2.918%) NaCl solution are given intravenously in the course of the experiment at the rate of 5 cc. every five minutes.

Time.	Urine in cc.	Remarks.
4.00	7.5	Thick chrome yellow, alkaline. No albumin. Injection begun.
4.15	2.5	Thick, chrome yellow, alkaline. No albumin.
4.30	7.5	Clearer. No albumin.
4.45	12.0 (?)	
5.00	23.0	Clear as water. Neutral to litmus. *No albumin* in any specimen.
5.15	36.5	
5.30	32.0	
5.45	27.5	
5.46	.....	Animal well. Released and killed by blow on head. Nothing abnormal noted on autopsy.

EXPERIMENT 89.—Belgian hare; weight 919 grams. Fed wheat and grass. *Snugly* tied into holder. Urine obtained with a soft rubber catheter. 105 cc. m/2 (2.918%) NaCl solution are injected intravenously in the course of the experiment at the rate of 5 cc. every five minutes.

Time.	Urine in cc.	Remarks.
3.15	4.0	Alkaline to litmus, thick, yellow. No albumin. Injection begun.
3.30	2.5	Somewhat clearer. No albumin.
3.45	20.0	
4.00	57.5	
4.15	40.0	Clear, colorless. Neutral to litmus. *No albumin* in any specimen.
4.30	39.0	
4.45	29.0	
5.00	37.0	

The following Experiments 90, 91 and 92 show that a mixture of different neutral salts, as represented by a RINGER solution, yields entirely similar results.

EXPERIMENT 90.—Belgian hare; weight 901 grams. Fed wheat and grass. *Snugly* tied into holder. Urine obtained with a soft rubber catheter. In the course of the experiment there are injected intravenously 135 cc. of a RINGER solution × 4,[1] at the rate of 5 cc. every five minutes.

Time.	Urine in cc.	Remarks.
1.40	4.0	Turbid, alkaline to litmus. No albumin.
1.45	.....	Injection into ear begun.
2.00	4.0	Turbid, alkaline to litmus. No albumin.
2.15	16.0	
2.30	38.0	
2.45	47.0	Clear, alkaline. *No albumin* in any specimen.
3.00	40.5	
3.15	32.0	
3.30	13.0	
3.45	7.0	Clear, neutral. *No albumin* in any specimen.
4.00	6.0	
4.05	No urine	Animal well. Returned to cage.

EXPERIMENT 91.—Belgian hare; weight 823 grams. Fed wheat and grass. Tied tightly into holder. Urine obtained with a soft rubber catheter. In the course of the experiment there are injected intravenously 125 cc. of a RINGER solution ×4, at the rate of 5 cc. every five minutes.

Time.	Urine in cc.	Remarks.
1.50	.....	Tied down.
1.55	.....	Injection into ear begun.
2.10	——	
2.25	3.0	Turbid, alkaline. *No albumin*
2.40	18.0	Clear, alkaline. *No albumin.*
2.55	13.0	
3.10	17.0	
3.25	20.0	Clear, neutral to litmus. *No albumin* in any specimen.
3.40	8.0	
3.55	4.0	
4.00	.....	Dies. Nothing abnormal noted at autopsy.

[1] The sodium, potassium, calcium chlorid mixtures that are known as RINGER solutions have a different composition with different authors. I used the following: NaCl 0.7, $CaCl_2$ 0.0026, KCl 0.035, and H_2O enough to make 100 cc. RINGER solution ×4 means four times this amount of salts in each 100 cc., a solution which has then about the same osmotic concentration as m/2 NaCl, as used in the previous experiments.

EXPERIMENT 92.—Belgian hare; weight 855 grams. Fed wheat and grass. Tied tightly into holder. Urine obtained with a soft rubber catheter. In the course of the experiment there are injected intravenously 150 cc. of a RINGER solution ×4, at the rate of 5 cc. every five minutes.

Time.	Urine in cc.	Remarks.
2.30	1.0	Turbid, alkaline. No albumin. Tied down and intravenous injections into ear begun.
2.45	1.7	
3.00	3.6	
3.15	11.0	
3.30	12.5	Urine clears until it looks like water. *No albumin* at any time.
3.45	21.0	
4.00	25.0	
4.15	23.0	
4.30	25.0 (?)	
4.45	9.5	
5.00	12.5	Clear, acid. *No albumin* at any time.
5.15	10.0	
5.20	.....	Killed. On autopsy nothing abnormal except that 25 cc. fluid are obtained from the peritoneal cavity!

Let us now retrace our steps and see what has happened so far as urinary secretion is concerned, for we were rather particular to emphasize that the ability of a kidney to secrete water was the best index of its functional activity. The experiments detailed above already suffice to show that *the secretion of urine*

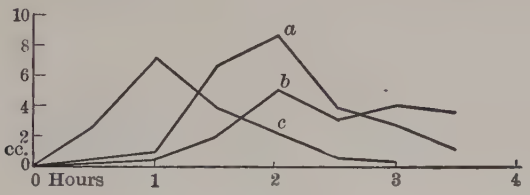


FIGURE 201.

from a nephritic kidney, or one threatened with a nephritis, tends to be maintained at a normal level or to be increased by the giving of various neutral salts, including sodium chlorid. We need but compare with each other the secretion curves of Figs. 202, 203 and 204 made by plotting time on the horizontal and the number of cubic centimeters secreted every fifteen minutes on the vertical and Experiments 84 to 92, upon which the curves are based. All the figures are drawn to the same scale.

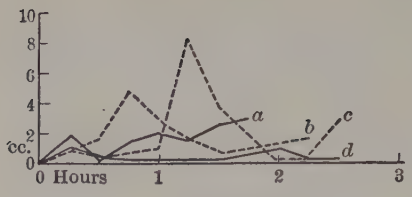


FIGURE 202.

Fig. 201 is introduced for comparison and shows normal urinary secretion in three rabbits loosely tied into an animal holder. The curves *a*, *b*, *c*, and *d*, of Fig. 202 (based respectively on Experiments 84, 85, 86, and 87) show, when compared with the curves of Fig. 201 how the secretion of urine is diminished when instead of being loosely tied into the animal holder the rabbits are so snugly tied down as to embarrass their respiration. *The diminished secretion gives way to an enormously heightened one if animals similarly treated are injected with a concentrated sodium chlorid solution.* Fig. 203 shows this. Curve *a* is taken from Experiment 89, curve *b* from Experiment 88. These experiments (as others to be described directly) show clearly that administration of sodium chlorid does *not* lead to a retention of water by the living animal.

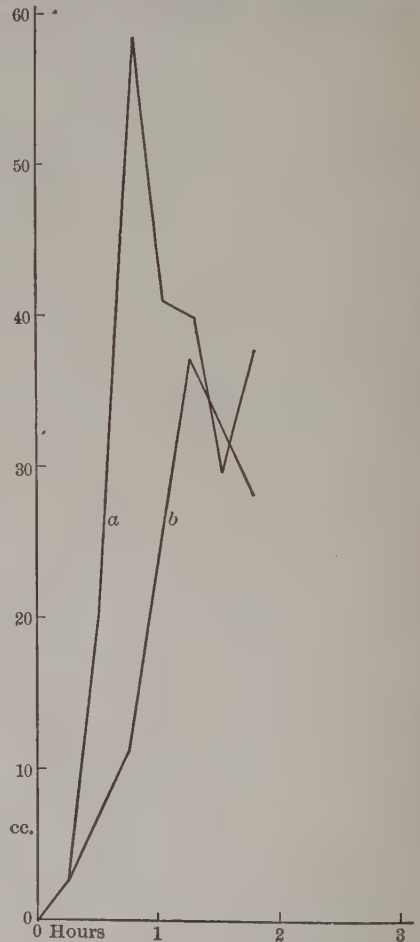


FIGURE 203.

Fig. 204 shows the curves obtained by injecting concentrated RINGER solution. Evidently all neutral salts (that have not specific poisonous effects) when injected in sufficient concentration increase the output of urine. The curves *a*, *b* and *c* are con-

structed respectively from Experiments 90, 91 and 92. These rabbits were again snugly tied into animal holders, but not only did none of them develop an albuminuria, but in conse-

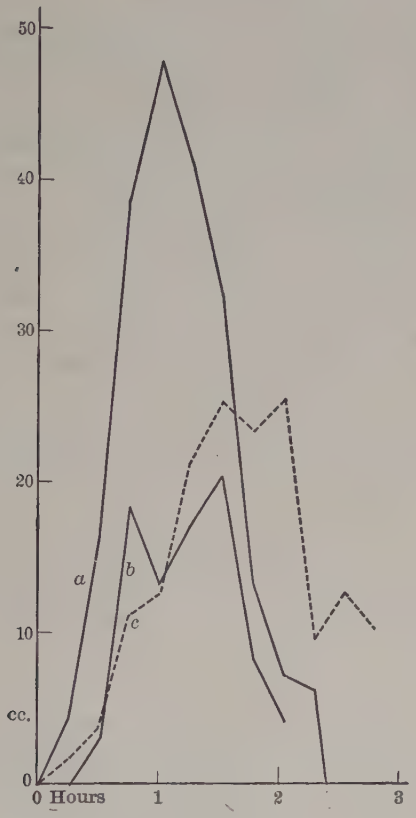


FIGURE 204.

quence of the injection of concentrated RINGER solution the urinary output was greatly increased in all.

3. Nephritis Produced by Injecting Acid

As the following experiment shows, *sodium chlorid when injected intravenously, in concentrated solution, simultaneously with a hydrochloric acid solution of a concentration found in Experiments* 60 *and* 61 (*pages* 491 *and* 492), *to lead to the symptoms of a most intense*

nephritis, practically suppresses this. The albuminuria scarcely appears, and there are no casts, no red blood corpuscles, no hemoglobinuria, no decrease in the amount of urinary secretion, and no general œdema.

Experiment 93.—Belgian hare; weight 2136 grams. Has been fed hay, oats, corn, and greens. In the course of the experiment there are injected intravenously at a uniform rate 140 cc. of the following mixture: 150 cc. n/10 HCl + 4.666 grams sodium chlorid and enough water to make the whole up to 160 cc. This yields a final solution, that is m/2 (2.918%) so far as the sodium chlorid is concerned. Urine obtained with a catheter.

Time.	Urine in cc.	Remarks.
3.30	.....	Fastened into animal holder. Catheterized.
3.45	.....	Injection into ear begun.
4.00	0.3	Slightly turbid, neutral to litmus paper. No albumin. No casts.
4.15	17.0	Clear as water, barely reddens blue litmus paper. No albumin. No casts.
4.30	61.0	Clear, barely affects blue litmus paper. Faint shimmer of albumin! No casts!
4.45	64.5	Urine clear, barely affects blue litmus paper. Faint trace of albumin. No casts. No hemoglobinuria at any time. No red blood corpuscles.
5.00	58.0	
5.15	38.0	
5.18	1.0	Dies.

Total amount of urine secreted since beginning injection 239.8 cc.

Autopsy.—Weight 2035 grams! Nothing abnormal is noted. The body cavities contain no fluid. The blood seems to coagulate abnormally rapidly.

It might be insisted in criticism of this experiment, that while sodium chlorid is thus able to counteract the effects of an acid in producing a nephritis, it cannot relieve such after once being established. This criticism is met in Experiment 94, in which a nephritis is first induced by injecting (practically) pure acid, after which its relief is brought about by injecting m/2 (2.918 per cent) sodium chlorid.

Experiment 94.—Belgian hare; weight 2343 grams. Fed hay, oats, corn and greens. Urine obtained with a soft rubber catheter. In the course of the first $1\frac{1}{4}$ hours of the experiment there are injected at a uniform rate 125 cc. of the following mixture: 120 cc. n/10 HCl plus 8 cc. 2/m NaCl, in consequence of which all the signs of a nephritis develop. For the acid mixture is then substituted a pure m/2 (2.918%) NaCl solution of which, up to the end of the experiment, there are injected 125 cc. With the change in the character of the injection fluid the signs of the nephritis are seen to disappear.

Time.	Urine in cc.	Remarks.
2.45	5.0	Catheterized. Turbid, light yellow, faintly alkaline to litmus paper. No albumin. No casts.
3.00	1.5	Weighed. Tied to animal holder. Intravenous *injection of acid mixture into ear begun.* Urine turbid, light yellow, faintly alkaline to litmus paper. No albumin. No casts.
3.15	0.7	Urine neutral to litmus paper. No albumin. No casts.
3.30	—	
3.45	2.1	Urine neutral to litmus paper. No albumin. No casts.
4.00	10.0	Urine faintly acid. Albumin. Isolated casts. Epithelial cells and red blood corpuscles.
4.15	7.0	Urine has a pink tinge. More albumin. Numerous casts and a larger number of red blood corpuscles. Injection of acid mixture stopped. *Injection of* m/2 NaCl *begun.*
4.30	20.0	Urine decidedly red (hemoglobinuria). Albumin content still rising. Fewer casts and red blood corpuscles.
4.45	42.0	Pink color to urine. Albumin decreasing. No casts can be found after long search of sedimented urine.
5.00	60.0	Pale pink. Albumin decreasing. No casts or red blood corpuscles.
5.15	53.0	Like water. Barely visible trace of albumin. No casts or blood corpuscles.
5.30	32.0	Like water and neutral to litmus paper. No albumin. No casts. No blood cells. *Injection stopped,* as animal has embarrassed respiration.
5.35	11.0 (?)	Some urine accidentally lost as animal dies. No albumin. No casts. No blood cells.

Autopsy.—Weight 2342 grams. Nothing abnormal in any of the organs. The peritoneal cavity is wetter than normal. The pericardial and pleural cavities are empty.

A number of interesting facts come to light in the two experiments just detailed. Let us first ask about the output of urine. In Fig. 205 we find in the curves *a* and *b* (Experiments 60 and 61) a graphic representation of the amount of urine secreted when n/10 hydrochloric acid (in m/8, that is, 0.729 per cent sodium chlorid, added to reduce somewhat the hemolytic action of the acid) is injected intravenously. When we compare these curves with those of Fig. 201 (normal secretion in rabbits), we notice that in spite of the great injection of water, the urinary output lies below the normal. The presence of the acid along with the water brings it to pass that the water is retained in the body; in other words, an œdema develops. The same factor, therefore, which we are holding responsible for certain of the kidney changes in neph-

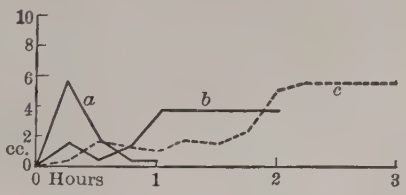


FIGURE 205.

ritis, is responsible for one of the most prominent symptoms of such kidney disease, namely, the œdema.

How enormously the urinary output is increased if a concentrated sodium chlorid solution is injected along with the hydrochloric acid is apparent when Fig. 206, drawn to the same scale, is compared with Fig. 205. And when we look through the protocols we find that this increased urinary output is associated with a loss of weight by the animal, in other words, a failure to develop an œdema, or the reduction or total disappearance of such as may be existing. Clearly, therefore, *salts, including sodium chlorid, all tend to reduce œdema,* as I have previously insisted.

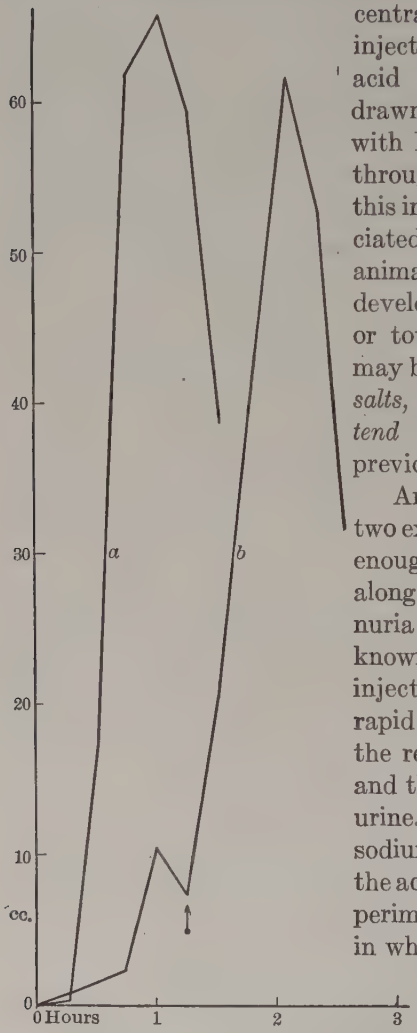


FIGURE 206.

Another point of interest in these two experiments is the fact that when enough sodium chlorid is injected along with the acid, the hemoglobinuria fails to develop. As is well known, a pure acid solution when injected intravenously leads to a rapid and extensive destruction of the red blood corpuscles (hemolysis) and the escape of hemoglobin in the urine. The only reason why *some* sodium chlorid was given along with the acid injections in the various experiments described in this volume, in which the effects of the pure acid on the kidney were particularly sought, was to escape in part this so great dissolution of the red blood corpuscles. When enough sodium chlorid is added the hemolytic action of the acid is avoided altogether, as Experiment 93 shows. This fact is of interest and importance, not only because it teaches

us that by increasing the salts in the diet we can relieve the signs and symptoms of paroxysmal hemoglobinuria,[1] but because it was a result to be expected if a theory of hemolysis which I have previously advanced[2] should be correct.

Incidentally, the last two experiments in conjunction with Experiments 59, 60 and 61 (pages 490 to 492) serve to meet a criticism that might have been raised against the experiments on asphyxial nephritis, in which it might have been said that the great urinary secretion obtained after injecting salt solutions was due *merely* to the injection of so much water.

4. Nephritis Due to Temporary Closure of the Renal Vessels

As Max Herrmann first showed, direct interference with the blood supply to the kidney leads to very destructive changes in this organ in an incredibly short space of time—the output of urine falls or may be stopped entirely and albumin, casts, and blood are found in such as is secreted. If the kidneys are examined they are found swollen, maybe grayish, and to present varying degrees of hemorrhage into the kidney substance. The following experiment illustrates this:

Experiment 95.—Belgian hare; weight 2335 grams. Fed hay oats, corn, and greens. Urine obtained with a catheter. The right renal artery and vein, and the left renal artery are clamped for one-half hour.

Time.	Urine in cc.	Remarks.
2.05	.....	0.008 gram morphin hydrochlorid given subcutaneously.
2.15	15.0	Clear, brownish-yellow, faintly acid to litmus. No albumin. No casts. After catheterizing the animal is weighed.
2.50	.....	Tied into holder.
3.00	0.5	Right renal artery and vein and left renal artery are clamped.
3.15	——	
3.30	.....	Clamps removed.
3.45	——	
4.00	——	
4.15	1.0	Much albumin. Hyaline casts and red blood corpuscles.
4.30	——	
4.45	0.5	Thick, turbid, acid to litmus. Full of albumin and casts.
5.00	0.8	Same
5.15	——	
5.30	0.8	Thick, turbid, acid to litmus. Full of albumin and casts.
5.31	.....	Animal appears well, is killed.

Autopsy.—Kidneys are swollen and deep red, but otherwise show nothing strikingly abnormal to the naked eye.

[1] Oscar Berghausen: Arch. Int. Med., **9**, 137 (1912).

[2] Martin H. Fischer: Kolloid-Zeitschr., **5**, 146 (1910) and page 438 of this volume.

The urinary output in this experiment is illustrated in curve *c* of Fig. 207. Let us now see how an animal similarly treated fares if it receives an intravenous injection of a "physiological" m/8 (0.729 per cent) sodium chlorid solution. Such an experiment serves to answer two important questions. First, is the giving of water to a case of "acute nephritis" dangerous because it "throws work on the kidney" and we need to "protect" this organ against doing any work; and second, does the administration of sodium chlorid aggravate such a nephritis because, as some say, it "further increases the work of the kidney" or because it "irritates" this organ? A no inconsiderable portion of the therapeutic world to-day insists on both restriction of water and of sodium chlorid in cases of acute nephritis. That both may be given and that the sodium chlorid, far from adding itself as a factor of evil to the water, really counteracts the only bad effects this has (through favoring the swelling of the kidney and washing out salts) is shown by the results of Experiment 96.

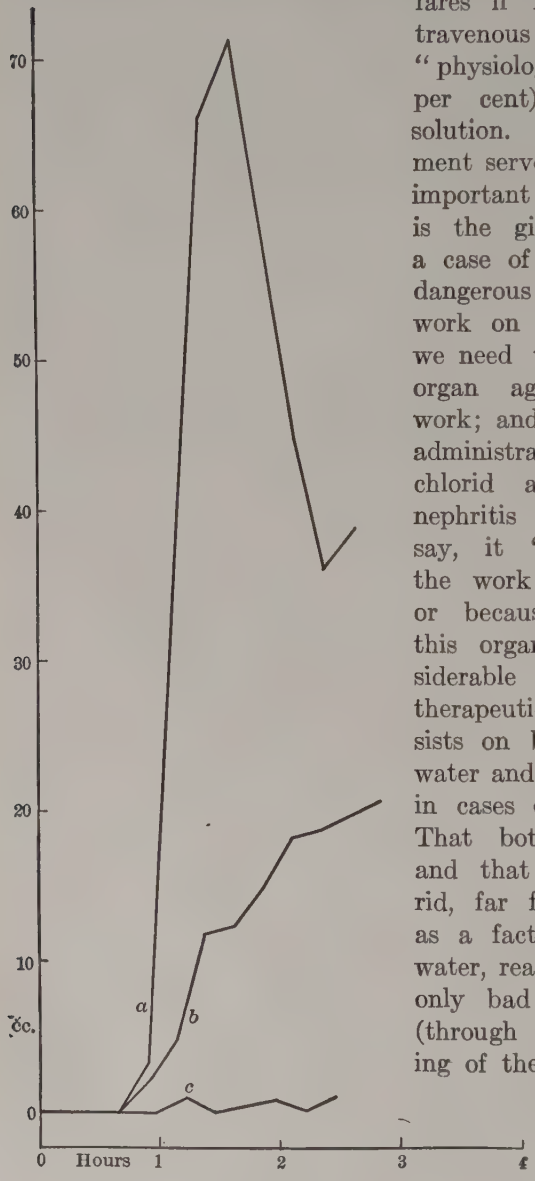


FIGURE 207.

EXPERIMENT 96.—Belgian hare; weight 2184 grams. Fed hay, oats, corn, and greens. Urine obtained with a catheter. The right renal artery and vein, and the left renal artery are clamped for one-half hour. Thereafter, 215 cc. of m/8 NaCl solution are injected at a uniform rate intravenously.

Time.	Urine in cc.	Remarks.
11.20	.....	0.016 gram morphin hydrochlorid given subcutaneously.
11.40	2.0	Thick, yellow, turbid, acid to rosolic acid. No albumin. No casts. Catheterized and weighed.
12.10	2.0	Same. Right renal artery and vein and left renal artery clamped.
12.25	——	
12.40	——	Clamps removed.
12.50	——	Injection of m/8 NaCl into ear begun. Accident to needle interrupts injection for ten minutes.
1.05	2.0	Full of albumin, epithelial, finely granular and hyaline casts.
1.20	4.7	Acid to rosolic acid. Full of albumin, epithelial, finely granular and hyaline casts.
1.35	12.0	Clear as water. Albumin going down. It is noted that there is decidedly more albumin in this experiment than when m/2 NaCl is used, volume of urine duly considered.
1.50	12.5	Decided drop in albumin. Still some casts.
2.05	15.0	Clear as water. Albumin present in traces only. Occasional cast only.
2.20	18.5	Same. Trace of albumin visible after standing.
2.35	19.0	
2.50	20.0	No albumin. No casts.
3.05	21.0	
3.06	.....	Killed.

Autopsy.—Weight 2269 grams. 6 cc. fluid in peritoneum. Pleural and pericardial cavities dry. Nothing abnormal noted in any organ.

The increased urinary output, in consequence of the injection of the m/8 sodium chlorid solution, is clearly evident when curve *b* of Fig. 207, based on this experiment, is compared with curve *c* obtained in the previously described Experiment 95. We note, moreover, that with the concentration of sodium chlorid employed in Experiment 96 a not inconsiderable amount of the injected water is retained, in other words, the animal develops an œdema. Many clinicians who believe that sodium chlorid "leads to œdema" might be inclined to say that this experiment supports their contention. That it does not is shown by Experiment 97, in which an animal, again rendered nephritic by clamping the renal vessels, is again injected with the same amount of water at the same rate, but the concentration of the sodium chlorid is further increased (to m/2 NaCl, that is, 2.918 per cent). As the protocol and curve *a* of Fig. 207 show, the urinary output under such circumstances is still

further, really enormously, increased, and not only does no œdema develop, but the animal actually loses in weight. To the interpretation of these various findings, which it was entirely possible to predict, we shall come immediately.

EXPERIMENT 97.—Black rabbit; weight 2778 grams. Fed hay, oats, corn, and greens. Urine obtained with a catheter. The right renal artery and vein, and the left renal artery were clamped for one-half hour. Thereafter, the animal received at a uniform rate an intravenous injection of 170 cc. m/2 (2.918%) sodium chlorid solution.

Time.	Urine in cc.	Remarks.
1.55	.....	0.016 gram morphin hydrochlorid are given subcutaneously.
2.20	14.0	Yellow, turbid, alkaline to litmus. No albumin. No casts. After catheterizing, the animal is weighed.
2.45	2.3	Yellow, clear, alkaline. No albumin. No casts. Right renal artery and vein and left renal artery are clamped.
3.00	——	
3.15	——	Clamps removed.
3.25	——	Intravenous injection of m/2 NaCl begun.
3.40	3.5	Filled with casts and red blood corpuscles. Fairly sets with albumin.
3.55	32.5	Last portions clear as water.
4.10	68.0	
4.25	73.0	
4.40	59.0	Clear as water. Acid to phenolphthalein, alkaline to rosolic acid. Faintest trace of albumin only. No casts. Occasional red blood corpuscles.
4.55	46.5	
5.10	37.0	
5.25	39.5	
5.26	?	Animal killed. Approximately 10 cc. urine lost in interval between stopping injection and making autopsy.

Autopsy.—Weight 2554 grams! 19 cc. fluid found in peritoneal cavity. Pleural and pericardial cavities are dry. Kidneys are slightly grayish.

Experiment 98 shows for what a long period the blood supply to the kidney may be cut off and yet the dangers ordinarily incident to such a procedure (partial to complete suppression of urine) be reduced by giving a concentrated salt solution. The experiment was really undertaken to indicate how the so-feared consequences of temporary occlusion of the blood vessels in operations on the kidney may be largely avoided or overcome—a discussion to which we shall return later.

EXPERIMENT 98.—White and blue rabbit; weight 2344 grams. Fed hay, oats, corn, and greens. Urine obtained with a catheter. The right renal artery and vein and the left renal artery and vein are

clamped for 1½ hours. After an interval, 90 cc. m/2 NaCl are injected at a uniform rate intravenously.

Time.	Urine in cc.	Remarks.
9.20	.....	0.016 gram morphin hydrochlorid are given subcutaneously.
9.50	.....	Tied down. Catheterized.
10.05	1.3	Deep brownish-yellow. No albumin. No casts. Renal blood vessels are clamped.
10.20	——	
10.35	——	
10.50	——	
11.05	——	
11.20	——	
11.35	——	Clamps removed.
11.50	——	
12.05	——	
12.20	——	
12.35	——	
12.50	——	
1.05	——	
1.20	——	
1 35	——	
1.55	——	*Injection of* m/2 NaCl *into ear begun.*
2.10	——	
2.25	0.3	
2.40	0.4	Filled with albumin and hyaline casts (exclusively).
2.55	0.4	
3.10	0.8	
		Injection stopped.
3.25	2.6	Urine clearer. Filled with hyaline and granular casts.
3.40	2.8	Casts fewer.
3.55	1.5	No casts.
3.55 to 5.25	11.3	No casts. Red blood corpuscles found (traumatic).
5.40	1.5	No casts.
5.41	.....	Killed.

Autopsy.—Weight 2300 grams. 10 cc. fluid in peritoneal cavity. 1.2 cc. in right pleural cavity. Left unusually moist. Kidneys soft and somewhat gray.

The secretion of urine in this experiment is represented graphically in Fig. 208. The first arrow indicates the point in the experiment when the clamps were removed. Up to the point of the second arrow no urine was obtained. At this time the sodium chlorid injection was started. The secretion of urine began less than half an hour afterwards.

5. Interpretation of Experimental Findings

It behooves us now to study the experiments just described in order to discover the *principles* that underlie the results obtained, for only by knowing these can we hope to put them to any intelligent therapeutic use. In the light of the facts developed in

the earlier pages of this volume it follows that the living organism represents in the resting state a series of colloids saturated with water. The slight (normal) secretion of urine observed in an animal which is quietly tied into an animal holder represents a certain amount of "free" water still available for secretion. When we tie such a normal rabbit into an animal holder sufficiently snugly to interfere with its easy respiration the urinary output falls, as shown in Fig. 202. This is because by such means the accumulation of carbonic and other acids in its body is favored, which increases the capacity of the body colloids for holding water. None is therefore left over to be secreted as urine. The animal is, in other words, at once put into a condition similar to that attained after several hours if it is simply kept off food and water. Parenthetically we may add that a similar asphyxial state, induced here by tying the animal into a holder, is obtained by chemical means when we give a dose of morphin, cocain, atropin, or arsenic, an anesthetic like chloroform or ether, an excessive dose of alcohol, or a nitrite.

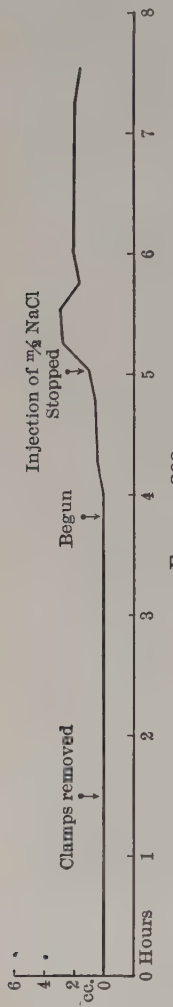


FIGURE 208.

The same increased hydration capacity of the kidney colloids and the body colloids generally is produced if we inject acid intravenously. The acid acts upon them and they therefore absorb and hold on to any water that may be given to them in these experiments along with the acid. Again none remains over to be secreted by the kidney. The animal retains the water and increases in weight, in other words, it develops an "œdema."

To the relief of all these conditions comes the administration of salt (along with the water). The salts—including sodium chlorid—reduce the amount of water that can be held by the body colloids generally, and so this freed water now becomes

available for urine. The kidney itself shares in this process and by shrinking admits a better circulation to be once more established through it. The body now loses water, and so the animal loses weight, in other words, the œdema disappears. The kidney proteins become less soluble and so the albuminuria goes.

Following a sudden apparent increase in number, the casts go. The apparent increase is due to the shrinkage, under the influence of the increased salt concentration, of the casts as they lie in the kidney tubules, followed by their easier and sudden washing out by the increased urinary flow. They tend, moreover, to change from the hyaline type to the granular, the latter representing reconversions from the hyaline under the influence of the salt.

6. Inhibitive Effects of Alkaline Salts on the Albuminuria of Hard Work

We shall conclude this section by giving a concrete illustration of the fact that, by increasing the alkali-salt content of the body, the opportunities for the development of the signs of a nephritis are greatly reduced. For such a test the albuminuria that develops in athletes after hard work was used, and with the following results:

In Experiment 63 on page 493 were detailed the quantitative findings regarding the excretion of albumin during an ordinary match basket-ball game, as determined by collecting the urine over the period of an hour and a half, in which time the game was played. In the following two experiments the urine was similarly collected, every precaution being taken to have the conditions for collection, regarding time, etc., as nearly the same as in the control. The athletes were under no restrictions regarding diet, the only difference being that in the two experiments now to be detailed, they took in addition to their ordinary food the juice of six sweet oranges in the first, and twelve in the second. The six oranges were consumed in the course of three hours preceding the game; the twelve in the twelve hours preceding the game. Oranges were chosen not alone because they are palatable and so offer no difficulty in having the men take them, but because the salts contained in them have not only a decided capacity for combining with stronger acids but because the

citrates, malates, etc., are the very salts which act most powerfully in reducing the solubility of proteins in acids (the swelling of organs, etc.). The game played in Experiment 99 was decidedly harder than that detailed for control purposes in Experiment 63, that of Experiment 100 fully as hard. The first five players were the same in all these three games, though the order in which they are numbered is not the same.

EXPERIMENT 99.—Juice of six oranges fed the players. Urine collected for period of $1\frac{1}{2}$ hours, during which time the play occurred. Phosphotungstic-hydrochloric acid-alcohol reagent used in the ESBACH albuminometer.

BEFORE THE GAME

Player.	Urine in cc.	Nitric acid test.	Heat test.
1	232	Negative	Negative
2	72	Negative	Negative
3	30	Negative	Negative
4	85	Negative	Negative
5	280	Negative	Negative

AFTER THE GAME

Player.	Urine in cc.	HNO_3 test.	Heat test.	ESBACH reading.	Albumin excreted, in grams.
1	62	Positive	Positive	1.25	.078
2	17	Positive	Positive	1.5	.025
3	152	Positive	Positive	0.75	.114
4	42	Positive	Positive	0.75	.132
5	228	Positive	Positive	less than 0.2	.046
					Av. .079

EXPERIMENT 100.—Juice of twelve oranges fed each of the players. Urine collected for period of $1\frac{1}{2}$ hours, during which time the play occurred. Phosphotungstic-hydrochloric acid-alcohol reagent used in ESBACH albuminometer.

BEFORE THE GAME

Player.	Urine in cc.	Nitric acid test.	Heat test.
1	73	Negative	Negative
2	170	Negative	Negative
3	187	Negative	Negative
4	6	Negative	Negative
5	23	Negative	Negative
6	62	Negative	Negative

After the Game

Player.	Urine in cc.	HNO_3 test.	Heat test.	Esbach reading.	Total albumin excreted, in grams.
1	97	Positive	Positive	0.75	.073
2	56	Positive	Positive	1.25	.070
3	11	Positive	Positive	1.6	.018
4	44	Positive	Positive	1.3	.057
					Av. .054
5	44	Positive	Positive	0.6	.028
6	45	Positive	Positive	0.25	.011

Player number 5 played first half only; number 6, second half only.

Even when we count out the player in the control game who started with an albuminuria, and those in the succeeding games who did not play through, we still find that *the albumin excretion, both so far as average concentration and average absolute amount is concerned, is decidedly lower after feeding citrus fruit than without such feeding.*

XI

ON THE TREATMENT OF NEPHRITIS

1. Introductory Remarks

For the treatment of nephritis everything has been suggested from prayer to hot irons down the back. A discussion of the subject can therefore scarcely bring the mention of anything new that might be tried. It can hope to be of interest or importance only as, on the basis of the views entertained by an author regarding the nature and the cause of nephritis, he will assign to certain practices grades of importance different from those assigned to these same practices by another — a difference of opinion that may perhaps be carried to the point where the one will find virtue in procedures that another regards only as evil, and vice versa. Were we to formulate a general rule for the prophylaxis and for the treatment of nephritis we should evidently have to say that this lies in *an avoidance and removal as far as possible, of every condition that favors the abnormal pro-*

duction or accumulation of acids in the kidney, or of such other substances which in their effects on the colloids behave like acid.

It therefore becomes necessary in approaching any case of nephritis first to get as clear a conception as possible of *all* the factors conspiring toward the production or maintenance of the abnormal content of acid and like substances in the kidney. Rarely shall we find but one factor active. To the toxic cause of a scarlatinal nephritis may be added that of an inadequate lung ventilation if the patient develops a bronchopneumonia. To the toxic nephritis of a pneumococcus infection already aggravated by a decrease in available lung for respiratory purposes, may be added an additional item if the patient develops a convulsion and so (through muscular work) produces suddenly an enormous additional amount of acid. The eclamptic patient who has just managed to drag through the last weeks of pregnancy faces death when the muscular efforts of labor or of a convulsion add more acid to that resulting from the intoxication of pregnancy. The patient with subacute or chronic nephritis, who, with persistent œdema, some casts, albumin and a deficient output of urine, is permitted or insists on working about the ward, may be breaking the camel's back with this added straw of acid production by even such light muscular work.

After we have, through restriction of muscular and mental effort, through rest in bed, through an adequate supply of fresh air, etc., removed as many of these conditions as possible, we turn our attention to combating those which we cannot remove. The rule to be followed then may be summarized in these words: *Give alkali, salts, and water.* To this may be added a fourth bidding: *Give dextrose* (glucose) or, if the conditions for its proper utilization are present in the body, some other sugar or starch. The reasons for all this are, of course, apparent. The *alkali* is given to neutralize the acid present in abnormal amount in the kidney (and the other œdematous organs of the body). The *salts* are indicated (and sodium chlorid is no exception) because the various changes induced in such colloids as constitute the kidney by the action of acid upon them, are counteracted by adding to such acid any salt, even a neutral salt. We need to give *water* in order to have this present in the body over and above the amount necessary to saturate all the body colloids; otherwise we shall have no " free " water left over out of which to make

urine. *Dextrose* or other carbohydrates are necessary, not alone from a chemical point of view, in that an abnormal production and accumulation of acid in the body is frequently the consequence of carbohydrate starvation, but because the sugars are peculiarly powerful in reducing certain types of increased hydration in proteins not produced by acids.

The exact methods to be adopted, the aggressiveness and persistence with which this simple rule is followed, and the results obtained by so doing must evidently depend upon the condition or combination of pathological conditions that our patient may have developed, and which we hold responsible for the abnormal production or accumulation of acid and like substances in his kidneys. Evidently an anesthesia nephritis with suppression of urine will call for a more aggressive therapy than a nephritis secondary to a slowly progressing arteriosclerosis. On the other hand, if we succeed in getting our first nephritic over his immediate kidney symptoms we may make a hopeful prognosis, for when he has exhaled his anesthetic he has rid himself of the condition that was responsible for the abnormal acid content in his kidneys. But in our second nephritic so hopeful a prognosis cannot be made, for while we may also benefit him, he continues to carry the original condition that brought him to us—his arteriosclerosis—even after we have treated him.

2. Diet in Nephritis

We have long paid attention to the diet in nephritis. Clearly, the direct consumption of acid as such by the nephritic is contraindicated. The mineral acids which would be worst in this regard do not enter into our foods to any appreciable extent, though in the forms of fruits, sour wines, etc., not inconsiderable amounts of organic acids are swallowed. With the exception of benzoic, oxalic and tartaric acids, most of these undergo oxidation in the body rather easily, being converted into carbonic acid, which is readily excreted. The organic acids are therefore less poisonous than might at first appear. But from this is not to be concluded that they are of no importance at all. Not only are certain "weak" organic acids (notably, tartaric, acetic, and lactic) quite as active *physiologically* as the "stronger" acids, but consumed in excessive amounts they are not without

effect even in "normal" individuals, as witness the œdemas observed in children that are fed buttermilk,[1] the urticarias following the consumption of excessive amounts of grapes,[2] etc. In nephritics these organic acids assume a yet more important rôle, for these individuals have, for various reasons, a decidedly decreased capacity for properly oxidizing them.

Still it is not to be concluded that every article of diet which yields some of these organic acids is therefore at once to be excluded. Such measures all too often lead to the absurd food restrictions with which patients are constantly tortured. Their importance need only be recognized to the end that an adequate amount of alkali, for example an alkaline water, be fed along with the food containing the organic acids.

In the metabolism of *proteins* not inconsiderable amounts of acid are produced.[3] Herein is to be sought at least part of the explanation of why a restriction of the proteins in nephritis is of use. If improperly used in the body, the proteins may, moreover, yield other than the normal amins, in other words, toxins which like acids are capable of increasing the hydration capacity of the body proteins and otherwise influencing their state. In the absence of sufficient carbohydrate, the fats may also yield abnormal or abnormally great amounts of such acids as diacetic, beta-oxybutyric, etc. But before one proceeds to a too drastic revision of the dietary, a process in which we are particularly liable to eliminate the proteins too vigorously, the absolute amounts of acid formed by the various constituents of the food should be considered. When this is done it will be found that the evil consequences expressed in terms of a *direct* acid yield from the proteins of our food, for example, are small compared with those that may be calculated from a bottle of dry wine. Consideration of the acid content of alcoholic beverages

[1] Ernst Schloss: Deut. med. Wochenschr., No. 22 (1910). Schloss does not, however, consider this an œdema due to feeding acid, but as "idiopathic." He found it to disappear on administering calcium salts.

[2] Personal observation. The urticaria disappears as soon as calcium salts are given, or fails to appear if such are consumed with the grapes.

[3] G. von Bunge: Zeitschr. f. Biol., **10**, 111 (1874); N. Lunin: Zeitschr. f. physiol. Chem., **5**, 31 (1881); Emil Abderhalden: Biochem. Zentralbl., **2**, 257 (1904). See also the important studies on the balance of acid-forming and base-forming elements in food by H. C. Sherman and A. O. Gettler: Proc. Soc. Exp. Biol. and Med., **8**, 119 (1911); N. R. Blatherwick: Arch. Int. Med., **14**, 409 (1914).

helps us, moreover, to understand why some of these exercise a worse effect in nephritis than others. We have long recognized that the alcohol content is not alone responsible for the effects of alcoholic beverages in kidney disease, for while it is true that in large doses alcohol allies itself with the general anesthetics, small doses do not interfere with the oxidative reactions in the living cells, but rather favor these (and so kidney function). But whatever is fed, it is clear that all the acid effects of the food need not appear if we will take the precaution of seeing that the diet contains sufficient alkali to neutralize the acid.

Just as certain features of a dietary thus favor the development of a nephritis, so also do others counteract it. Most notable here are the long-observed beneficent effects that follow the use of *alkalies* and the substitution of a more strictly *fruit and vegetable diet* for our ordinary mixed diet. The bases present in fruits and vegetables are from the start combined with weak organic acids which in the body are largely oxidized to carbonic acid. How successfully a diet rich in fruits and vegetables counteracts even the normal tendency of the body to run toward the acid side is a matter of common knowledge to any physician who has watched the urine of his patients turn from its normal acidity to an alkalinity, when ordered from an ordinary mixed diet upon one richer in the vegetables and fruits.

But this neutralization capacity of the fruit and vegetable diet for acids is not the only factor which accounts for its beneficent effect. We learned earlier that the solubility of protein in any acid is markedly reduced by salts. Not only are the vegetables rich in salts, but they are rich in the very ones which act most powerfully in reducing the solubility of the protein. So we may find in this fact, along with what has already been said regarding the capacity of the vegetable diet to neutralize acids, a satisfactory scientific foundation for the reduction of the albuminuria in nephritis, when a diet rich in vegetables follows one in which these were not so abundant. Such salts also serve to reduce the size (swelling) of the kidney, and as we have seen, they practically prevent those precipitation effects in the kidney cells (granule formation) that are characteristic of the early changes of nephritis from a morphological point of view. Speaking generally, a diet high in fruits and vegetables also means that the individual is consuming more water. The

effect of this will be discussed later, but even now it may be pointed out that such will aid our nephritic, because it brings to his kidney the "free" water from which alone he can make urine.

Practically expressed, I let the nephritic eat pretty much as he pleases. In the ambulatory subacute or chronic cases associated with blood vessel disease or secondary to infections of the kidney I permit a moderate meat ration on condition that the patient will eat his vegetables first. This trick increases his alkali intake at the expense of the acid side of his dietary. The soups are not forbidden, because the salts and water thus consumed offset largely any bad effects which the accompanying meat extractives are imagined to have. If the proteins are thought to be giving rise to "autointoxication" products in the alimentary tract, I use small doses of calomel or occasional large enemas of salt solution, sodium bicarbonate or soap. Enemas of sodium bicarbonate (two level tablespoonsful in two quarts of warm—not hot—water) are especially to be recommended. Calomel in small doses does not injure the kidneys, but exercises only the dehydrating effect upon all the body colloids, which increases secretion from the alimentary tract and the kidneys. Since even large amounts of fruits and vegetables may not prove sufficient to keep the patient well supplied with alkali, I urge the daily use of sufficient natural or artificial alkaline waters, either carbonated or still, to accomplish this purpose. *A patient is getting enough alkali when his urine is kept persistently neutral to litmus.* He should be given neither more nor less than this amount. I teach the ambulatory nephritic to test his own urine and to increase or decrease his alkali intake as necessary.[1]

The bedridden cases are treated from a dietary point of view in the same fashion. More harm is done these patients by underfeeding them than by overfeeding. The caloric needs of the individual must be covered daily. A "starvation acidosis" is as bad as any other kind. Orange juice, grape fruit juice,

[1] To escape the effect of alkali upon the stomach and obtain it in the small intestine E. G. Ballenger and O. F. Elder (Jour. Am. Med. Assoc., **62**, 197 (1914)) suggest its administration in admixture with mutton suet and paraffin. They further make use of the clever expedient of adding a little phenolsulphonephthalein. The patient then knows that he is consuming enough alkali as soon as he voids a constantly pink urine.

lemonade, cereals, milk and cream, vegetables, fruits, and various meats and fish should in the order named be urged upon the nephritic. Such foods as will carry it should have sugar added to them, for the first items in which our diets are likely to be short are the carbohydrates.

These patients also are given an alkaline water of some sort. The natural or artificial alkaline spring waters are perhaps most easily borne. If the patient will tolerate it, 0.5 to 1.0 gram of sodium carbonate or sodium bicarbonate may be added to each glass of such alkaline water or to plain water. Some patients who cannot tolerate the carbonates will take sodium citrate, sodium tartrate,[1] sodium acetate or other salts of a strong base with a weak acid in half-gram or larger doses every hour, either when dissolved in water or in capsules followed by water. Calcium hydroxid can easily be given by mixing lime-water with milk. As the salts of the bivalent metals are particularly active in decreasing the hydration-capacity of the body-colloids, the administration of magnesium oxid or milk of magnesia up to the point where two or three easy movements of the bowels are obtained daily, gives good results. The soluble salts of calcium and strontium, as the iodids, acetates, lactates or citrates are to be highly recommended. They are, unfortunately, absorbed rather slowly, but once in the body they keep the hydration capacity of the body colloids low. The same is true for the salts of iron which the older doctors used so effectively.

For reasons discussed before, I do not think that table salt should be restricted in a threatened or developed nephritic, but on the contrary should be urged upon the patient. Food serves as a natural carrier for this. In the form of salt meats

[1] Tartaric acid is little, if at all, oxidized in the body. Its appearance in the body therefore draws upon the alkali contained therein and emphasizes the necessity of seeing to it that foods rich in this acid (as grapes) are accompanied by sufficient fixed alkali to do away with the acid effect. Underhill, Wells, and others have reported deleterious effects upon the kidneys from feeding tartrates, but W. E. Post (Jour. Am. Med. Assoc., **62**, 592 (1914)) noticed none when up to 24 grams were given to nephritics; in fact he noticed nothing but good results to follow the use of sodium and potassium tartrates—as the older doctors have so long known. William Salant (Jour. Am. Med. Assoc., **63**, 1076 (1914)) noticed poisonous effects in rabbits on an oat diet but not on a diet of carrots. But an oat diet as Weiske has shown is an "acid" diet and one insufficient in calcium. As Salant also observed, calcium administration does away with the poisonous tartrate effect.

and salt fish we can easily get considerable quantities of sodium chlorid into our patient, and by placing a salt shaker at hand, he can liberally increase his intake by dusting it on his vegetables, his fats, and such proteins as we allow him.

Through the diet alone we can, therefore, do a great deal to keep the intake of alkali and salts high.

3. Water Consumption in Nephritis

The question of water consumption resolves itself into two parts—into the use of water in cases where a nephritis is likely to arise, and into its use in an established case. The reasons are obvious why water needs to be given in the first instance and why we wish to give it at a uniform rate in the largest possible amounts that will not injure the patient. Not only must the patient get water in order to have the wherewithal to make urine, but, whatever the conditions lying behind the nephritis, the pathological state amounts in the end to an intoxication. This is strikingly true, of course, in the infectious diseases or in an eclampsia case. Here the whole organism is suffering from the effects of a poison. The effect of that poison depends not alone upon the length of time that it acts upon the organism as a whole or any individual part of it, but upon its *concentration* at any one time. If now our interest centers upon a toxic effect that such a poison may have upon the kidney, and we are anxious to protect this organ, it is clear that the concentration of the poison must be kept as low as possible in it. To do this only two possibilities are open, and when we cannot control the factor of poison production, we can hope to cut down the effect of the poison only by keeping what is produced as dilute as possible. This calls for the giving of water. In this connection the practical point should be remembered that in ordinary practice an ever so patient administration of water through the day is likely to be neglected in the night. As toxin production does not cease with nightfall, it is clear that water administration also should not, otherwise we are likely to lose in a few hours at night what we cannot subsequently regain in days, if at all. The administration of water cannot therefore be left to the haphazard desire of the patient. It must be insisted upon in a regular manner. A good rule is to give half a glass every hour *day and night.*

At this point we are likely to be met by the argument that while such a water therapy is accepted as advisable in the toxic nephritides, those associated with heart lesions, etc., are not to be similarly treated. Let us first point out that these too are toxic nephritides—the patient with a broken heart compensation, or a compressed lung due to a carcinomatous pleurisy, and albumin in his urine shows this (according to our views), because the acid content in his kidneys is abnormally high. The more the concentration of this can be reduced the less will be its effect on the kidneys. Thus far, therefore, he needs water quite as much as the nephritic who is such in consequence of an infectious disease.

But it has been argued that the giving of water increases the work of the heart in these cases, and so is bad. I have been unable to discover where this notion first arose. It is apparently somebody's clinical guess, for there exist no physiological proofs for such a belief. If it is reasoned that the work of the heart is increased because more water secretion calls for more filtration pressure and this in turn requires more blood pressure, and therefore more work from the heart, then the reasoning is technically correct. But if it is remembered that ten to fifteen millimeters of mercury pressure suffice for all this, then the maintenance of this fraction of the physiological average of one hundred and twenty-five millimeters required for all circulation purposes can hardly be looked upon as much of a burden to the heart. As a matter of fact it is the viscosity of the blood which determines in good measure the amount of work the heart must do in pumping it. The addition of water does not increase this, but decreases it.

If the whole matter is reduced to the simple statement that the giving of plain water may aggravate some of the signs of a nephritis (like the generalized œdema) then no quarrel is to be had with it. What is observed is not, however, the consequence of a little water administration upon cardiac activity.

The only objections that may be raised against a too vigorous administration of water are two. The first is associated with the fact that when the hydration capacity of any tissue has been increased (as that of the kidney in nephritis) the giving of water permits it to swell; the second with the fact that pure water in washing through the kidney washes out not only poisonous substances of which we would be rid, but good salts of various kinds in addition. Thus, it might be

reasoned that to give water in the acuter forms of nephritis would be to aid this swelling. Such swelling of the cells, so far as the *cells themselves* are concerned, can hardly be considered serious, any more than a moderate œdema of any tissue is in itself particularly destructive to the tissue. But in the case of the kidney a complicating circumstance arises which does make such a swelling dangerous. This resides in the fact that the capsule of the kidney is not as expansile as the rest of the kidney substance. As the kidney substance swells, this tends, therefore, to press upon the blood vessels and retard the circulation of the blood through the kidney. This condition actually comes to pass. Thus, a kidney already nephritic, say from the toxin of an infectious disease or an anesthetic, aggravates its state by hampering its own blood supply.

The washing out of salts from the kidney acts in the same direction, for, as already noted, these tend to counteract the swelling. Our problem might, therefore, seem to become that of balancing the good effects of water against certain bad ones. Actually it is much simpler. *We give the kidney the benefit of the virtues of water, while we protect it at the same time from the dangers associated therewith by giving along with the water properly chosen salts in sufficient amount.*

4. The Rôle of Salts in Nephritis

In our every-day diet we never seriously consider whether we drink distilled water, tap water, or a table water. And from this point of view we might be inclined to ignore the exact composition of the liquids consumed by a nephritic. But let us look at the problem a little more critically. The normal individual does not really with impunity ignore the matter. It only seems so. In his food he consumes large quantities of various salts, so what he really obtains in any longer interval of time is a salt solution. The proper regulation of this—that is to say, the continuous consumption of a proper salt solution which in its turn maintains a proper salt concentration in and about the various cells in the body—is accomplished through the "taste" of the individual. If his salt consumption has been too high, he craves fresh water, and so washes out the excess. If, on the other hand, he has lost too great an amount of salt

he consumes more and makes up the deficit. The truth of these statements is attested by the most varied scientific and social facts. The animal treated with a strong salt solution makes desperate efforts to get at water, and the salt-starved animal licks the sides of its cage and laps up its urine. The American retailer of beer feeds his customers salt meat and fish gratis. This gives them a thirst which they satisfy with beer, and overdrinking, they turn about and demand more salt food.

If these facts are borne in mind, it becomes easy not only to devise a therapy which from present evidence promises most in the relief of nephritis and allied conditions but to recognize the merits of long recognized therapeutic procedures.

The milk diet has, not without reason, been popular. By giving milk we give a patient a useful balanced ration of fat, carbohydrate, and protein. But we do more than this—we give water and salts. The water helps to wash out poisons and the salts contained in the milk have a concentration which just suffices to do away with the effects of giving an equal amount of water pure.

Similar reasoning explains the beneficent effects of giving "physiological" salt solution in large amounts by rectum, intravenously or subcutaneously, in various acute infections It is again the combined effects of much water to wash out poisons, and enough salt to counteract that accidentally lost [1] by the same process that washes out the poison. When in spite of such procedures the signs of a nephritis develop we need to press *more* salt (alkali and sugar).

In the nephritic, because of the accumulation of substances in parts or all of his kidneys or other organs, which increase their hydration capacity, these are abnormally swelled. To reduce their swelling a more than "physiological" concentration is demanded. To accomplish this the patient must consume a proportionately larger amount of salt. This is a matter which for various reasons we cannot leave to his taste alone. We need in consequence to give him specific instruc-

[1] We have become all too inclined to consider *everything* that comes out in the urine as something that the intelligence of the kidney has found harmful to the body. It is scarcely as wise as this. It is rather hard to see, for example, why, in a salt-starved animal that is being given water, the animal continues to eliminate some salt in the urine up to the moment of death, when *it is this very elimination that is killing the animal.*

tions as to how to increase his salt intake. As previously noted, sodium chlorid forms no exception to this rule. There are, however, many other and more powerfully effective salts, and herein lies the scientific reason for the so-long established custom of giving these patients the acetates, tartrates, citrates, etc., of sodium and potassium, as well as magnesium sulphate, magnesium citrate, BASHAM'S mixture, etc. These are all salts which in low concentration produce great dehydrating effects in all the tissues of the body. Such salts therefore permit us by keeping the hydration capacity of the body colloids low, to get the beneficent washing-out effects of water without its deleterious consequences.

5. More Aggressive Methods of Alkali and Salt Administration

Let us now imagine that in spite of these procedures the nephritic's symptoms do not improve. Many patients cannot long keep up a high consumption of alkali and salt by mouth. They may begin to vomit; or a "uremia" with vomiting may develop so that we may fail in our therapy. Or let us imagine that the symptoms are rather severe from the start, so that alkali and salt by mouth seem inadequate. What are we then to do?

We continue to get as much use out of the gastric route as we can, but we use the rectum also in order to get an absorption of alkali, salt and water.

Here again a more than "physiological" concentration of salt is demanded. A "hypertonic" solution is necessary. To reduce the œdema in the kidney or in the brain, in the optic nerve or in the tissues generally, we need to try to increase, at least temporarily, the absolute concentration of salt in the whole body. We therefore use a *hypertonic salt solution to which has been added an alkali. Obviously, when using such a hypertonic solution by rectum we do not allow pure water or any solution of low concentration to be taken by mouth.* The patient may wet his mouth to relieve his sense of thirst, but no more, otherwise we only reduce the concentration and so the therapeutic value of the solution we are administering by rectum.

After much experience I have found the following procedure most simple and effective and now use it more often than any other. If the attending physician will but consider the patient

as a mass of swollen protein and keep in mind that the signs and symptoms which he is asked to treat are but the expression of this swelling either in the mass as a whole or in some particularly affected part thereof, like a kidney—and that the methods for securing dehydration of the affected parts (and therewith of the signs and symptoms referable to that part) are limited in the light of our present knowledge to an attainment of water evaporation from the affected part and its effective dehydration through an increase in the content of alkali and salt in the affected part—he will recognize quickly the reasons for the following categorical rules.

1. *Stop all water by mouth* for as long a period as may be necessary. Six to eight hours may suffice, but if the symptoms still persist this period may be doubled or trebled.

2. *Give an (hypertonic) enema of baking soda water* (two rounded tablespoonsful of baking soda to two quarts of warm, *not hot*,[1] water). The injected solution may be rejected like any ordinary cleansing enema. A goodly amount of the strongly alkaline salt is nevertheless absorbed. Repeat the enema in two, three or four hours, depending upon the urgency of the case, and then every four, six or eight hours and finally night and morning only. The number necessary is determined by the state of the patient and by the reaction of his urine. Enough alkali must be given so that every specimen of urine is alkaline to litmus or methyl red paper.[2]

3. *Give a teaspoonful of saturated solution of magnesium sulphate by mouth every hour for six to eight doses.* This is the strongest dehydrating salt that is readily absorbable. While such a dose may produce catharsis this is not to be taken as the real index to the effectiveness of its action. It is the salt that is absorbed *into the tissues* that produces the effect desired and this may be obtained with no catharsis whatsoever.

How long must such therapy be persisted in? The alkali administration may be used indefinitely, analysis of the urine alone being an index to its quantitative efficiency. The index to an effective salting of the patient's tissues is found in a disappearance of his symptoms (better urinary secretion, awakening

[1] Sodium bicarbonate is decomposed to sodium carbonate at 70° C. (158° F.). The latter does no harm but is more irritating.

[2] See page 772.

from coma, decrease in intraocular tension) or, if conscious, in the development of *thirst*. The patient must obviously be kept in such a state of thirst—in other words, be permitted nothing but hypertonic salt and alkali mixtures (and when fed, as *dry* a diet as possible)—until sufficient time has elapsed to permit of the removal of those first pathological circumstances which led to the nephritis, "uremia" or glaucoma for which he summoned aid.

It must be clearly understood that there is nothing specific about the scheme of treatment just outlined. It only represents *one* method of producing an adequate alkalinization and salt dehydration.

A formula [1] which I employ more commonly when intravenous measures are necessary but which may be used by rectum and with good results is the following:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	10 grams
Sodium chlorid	14 grams
Distilled water, enough to make	1000 cc.

Simple as is this formula, care must be taken in its preparation if good effects are expected. While we need not for rectal use insist upon the same grade of care that is necessary when such a solution is to be injected intravenously, it is well to consider everything even here.

Sodium *carbonate* is used, not bicarbonate. The carbonate is physiologically more effective than the bicarbonate, for one of the acids which is produced in the body is carbonic acid, and sodium bicarbonate is already saturated with this. In consequence, it cannot act as a carrier for it.

The chemically pure, crystallized sodium carbonate ($Na_2CO_3 \cdot 10H_2O$) or the monohydrated form ($Na_2CO_3 \cdot H_2O$) is to be insisted upon. Two other forms of sodium carbonate are found in the market, the dry (Na_2CO_3), and the so-called dry or "dried." The "dried" salt found on the ordinary drug shelf contains approximately two molecules of water of crystallization ($Na_2CO_3 \cdot 2H_2O$). We are inclined to advise against all except the large crystallized form or the monohydrated form; but *whatever salt is used its content of water of crystallization must be remembered, otherwise a solution of a different strength from that which has been found most useful will be obtained.*

[1] This is the solution frequently called by my name.

The proportionate amounts of these four salts that may be used are to each other as their molecular weights, or, in definite terms:

10.00 grams $Na_2CO_3 \cdot 10H_2O$ (molecular weight 286) crystallized "sal-soda" =
4.95 grams $Na_2CO_3 \cdot 2H_2O$ (molecular weight 142) "dried" =
4.33 grams $Na_2CO_3 \cdot H_2O$ (molecular weight 124) "monohydrated" =
3.71 grams Na_2CO_3 (molecular weight 106) really "dry."

The sodium chlorid-sodium carbonate solution should be made up in *distilled* water and filtered. If the salts used are pure and the whole is properly prepared the resulting solution is perfectly clear.

Rectal Injection of the Solution.

Unless the patient is mentally incapable of comprehending what we say, it is well to explain to him before an injection is made just what we desire to accomplish and so secure his cooperation. As the solution is hypertonic and contains alkali in addition, it not only irritates the rectum somewhat, but leads temporarily to a secretion of water into the rectum while the salt and alkali are being absorbed.[1] The patient, in consequence, has a desire to go to stool, which after we have once permitted him to satisfy, we wish him to overcome. By obtaining his cooperation, the solution is retained for longer periods of time, or entirely, and correspondingly we get a more perfect absorption of the alkali and salt.

To inject the solution we may make use either of a continuous drip method, or inject larger quantities at varying intervals of time. It is not necessary first to cleanse the rectum locally, and especially are we *not* to try to accomplish this end by a previous administration of cathartics. These methods only increase the irritability of the rectum. It is well, of course, if the lower bowel is empty (as immediately after the patient has had a stool). But if no movement has occurred recently we make our injection just the same. Perhaps the patient will then have a stool from the alkali-salt solution injected. This cleans the rectum, and we begin again.

For administration of the alkali-salt solution the patient should first be comfortably arranged in bed. He should lie on

[1] No solution is absorbed or secreted "as such." See page 318.

his left side on a rather hard bed and with no pillow, or only a small one, under his head. His hips may be elevated slightly to give still greater pitch to the rectum, but this should not be attempted unless the patient can be made *perfectly* comfortable.

We are now ready to inject the solution, and may choose either the slow *drip method* or the *fractional instillation* method. The choice from the patient's point of view is about evenly divided between the two, and he should be consulted and his wish followed.

The *fractional instillation* method will be described first. For this the apparatus shown in Fig. 209 may be used. *A* is a funnel that has a capacity of not less than 250 cc. *B* is a soft rubber tube at the lower end of which is the pinch clamp *C*. *D* is a short glass tube that connects *B* with the soft rubber catheter or rectal tube *E*. The solution to be injected is heated to 40° C. (110° F.) and the patient being in position, the catheter is lubricated with petrolatum. Into the funnel are now poured 250 cc. of the solution, and the stop-cock is temporarily opened so as to drive the air out of the tube and catheter. The catheter is then gently inserted well into the rectum and the funnel is emptied by again opening the pinch-cock. The short glass tube will inform the operator when the last portions of the mixture are flowing into the rectum, when the hold on the pinch-cock is released. In this way no air will be allowed to enter the rectum and balloon it, and extra irritation from this source is avoided. If the patient's lower bowel has been empty, the injection is usually easily retained, and may be repeated in half or three-quarters of an hour. If the bowel was filled with fecal matter the first injection serves to bring on a movement, and the cleared bowel will subsequently absorb better. The injections may be repeated as often as the symptoms of the patient demand it, or until the patient finds them difficult or impossible to retain. A period of rest should then be given. If our case is so urgent that this cannot be allowed with safety, then the solution must be given intravenously (see below).

FIGURE 209.

For the *continuous drip method* the arrangement shown in Fig. 210 works well. *A* is an ordinary half liter or liter graduated irrigating vessel with a side tubulation. It connects through

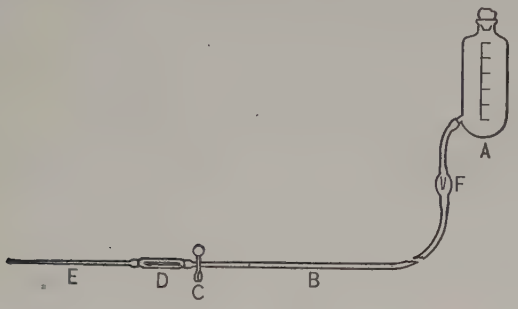


FIGURE 210.

the rubber tube *B*, carrying a pinch-cock *C*, with the glass insert *D*, in which lies a thermometer. The insert connects with the soft rubber catheter or rectal tube *E*. *F* is a glass insert which permits observation of the rate at which the solution is dripping into the rectum. From 1 to 4 drops a second should enter. This is about as high a rate as the patient can stand without rejecting the fluid. Roughly, this corresponds to an injection of from 240 cc. to 960 cc. per hour.

The injection fluid is retained best if it is delivered *into the patient* at not less than body temperature, and 40° C. (110° F.) is better. For this reason the thermometer in *D*, located as near the rectum as possible, is of great convenience. As the solution slowly passes out of *A* through the tube, it falls in temperature. The vessel *A* is therefore conveniently filled with the solution at a temperature somewhat above 40° C. Or one can set this vessel into a second one containing warm water, or place the tube *B* in warm water, or cover it with a blanket by way of maintaining the solution at a proper temperature as convenience and the ingenuity of the medical man dictate.

In hospital practice, thermostatic devices heated by electricity or gas may be conveniently installed.

Amount and Time Interval.

How much of the solution may be given by rectum and how long do we continue with it? The answer to this is found in the

condition of the patient. So far as I have been able to observe, no harm can be done by indefinite use of the solution. *A full physiological effect is obtained when the patient is kept free from the various signs and symptoms of nephritis, and the urine is persistently neutral in reaction toward litmus.* Such a reaction of the urine may be obtained in a few hours or it may take all day. It all depends upon the initial content of acid in the patient's body and the rapidity with which the alkali is being absorbed. A call for two to four liters in the twenty-four hours is none too much. Where a neutral urine is not obtained the efficacy of the therapeutic measures employed must be taken under review. If adequate and the patient can not be alkalinized the prognosis is bad irrespective of the nature of the pathological circumstances producing the acid intoxication. The symptoms may have cleared entirely even before the saturation of the body with alkali has been carried to the point where the patient secretes a persistently neutral urine. It is, however, unsafe to stop short of such a point or to allow the patient to swing back to the even normally acid side too early.

Individuals differ greatly in their behavior toward these injections. I have seen patients bear them for weeks at a time without complaining, and without ever rejecting them. Others will insist from the first that they cannot hold them. A few quieting words of explanation to the patient help much. It is well to point out that if these hypertonic salt-alkali mixtures are retained for any time at all, say even for an hour, they do much good. When at the end of such a period the patient rejects some fluid from the bowel, this is not the same as that which was introduced, simply minus a certain quantity that has been absorbed. Hypertonic sodium chlorid-sodium carbonate mixtures are not absorbed as such. The salt and alkali are absorbed out of the solutions while water is being secreted into the bowel. Therefore, if the solution is retained even for a short time, the patient will have increased his body-content of alkali and salt, which is the whole purpose of the therapy.

After the kidneys are functioning in a more normal way we may substitute for the hypertonic sodium chlorid solution one more nearly isotonic with the body fluids. A solution of sodium bicarbonate containing 12 to 14 grams to the liter of distilled water does very well. This is about equal in concentration to a "physiological" sodium chlorid solution and preferable to it, for

while not as powerful as the carbonate, sodium bicarbonate neutralizes acids stronger than carbonic and so helps to maintain the neutral reaction of the urine. Sodium bicarbonate may be injected in indefinite amounts without giving rise to rectal irritation. I use it much on this account in children and in protracted nephritides in adults, where I frequently raise the concentration to 18 or 20 grams to the liter.

The desire to introduce into the nephritic the bivalent metals which dehydrate the body colloids far more than do the univalent metals cannot be easily satisfied. The reason for this is obvious. Their carbonates and hydroxids are largely insoluble, and so the administration of bivalent metals such as calcium or magnesium along with carbonates or hydroxids is impossible. The only schemes that I have found of service are limited to patients with mild nephritis and to those recovering from the severer types, where lime water may be added to the milk consumed by the individual, or he be given magnesium oxid, milk of magnesia, and soluble calcium or strontium salts by mouth. For rectal injection a "physiological," 0.85 per cent sodium chlorid solution, to which 0.1 per cent calcium chlorid is added, also works well if alkaline solutions have not been used for some hours previously.

It is well here to consider the effects of the *sweating* so commonly practiced in nephritis. It has been used so long and with such good results that its usefulness cannot be doubted, and yet I question whether what it accomplishes is really correctly understood. For the most part sweating (as purging) is supposed to act as a partial or complete substitute for kidney function, it being held that with the sweat, poisonous substances which should be eliminated through the urine are carried off through the skin. Since the sweat chemically contains much the same sort of material as urine, this belief is, of course, partly justified, but even with copious sweating we get in the aggregate but little through the skin. *Sweating is an effective method of dehydrating the swollen body colloids* and the relief of coma, of headache, of high blood pressure due to cerebral œdema, of vomiting and CHEYNE-STOKES respiration and of a generalized œdema, together with evidence later of a better urinary secretion (following dehydration of the swollen kidney) a better general circulation, etc., are more logically explained through this dehydration than on the older basis which held that "nephri-

tic toxins" assumed to be responsible for these various signs are thus lost vicariously through the skin. Sweating dehydrates all the organs of the body and permits a better circulation to take place through them.

It is self-evident how sweating may relieve a swollen kidney and how in the end it therefore accomplishes what alkalinization and increase in salt concentration are trying to do. Only in sweating two things must be kept in mind. While it is true that by this means we dehydrate the body tissues, sweating does nothing to meet the causes for the increased colloid swelling. Second, when we carry off water through the skin (or bowel) we must not expect the same water to be able to come through the kidney. *Diuresis follows sweating only secondarily.* Only when after the shrinking consequent upon the sweating a better blood supply has been assured the kidney may this recover sufficiently to be able to put out later water brought to it in a "free" state.

6. The Treatment of Severe Cases of Nephritis

Under this heading we shall consider those patients in whom we encounter such especially alarming signs and symptoms as great or complete suppression of urine, rapidly progressing optic-nerve changes, persistent headache and nausea, vomiting, convulsions, stupor and coma, great quantities of albumin in the urine, etc.

While we realize that a complete explanation of the nature and of the cause of these various clinical signs cannot be summed up in any brief statement, we believe that as previously emphasized, an essential, if not the essential element in all of them is an œdema of the affected part. This œdema is represented physico-chemically by an increased colloid swelling of the tissues involved, and as responsible for such, we hold the abnormal production or accumulation of acid in the part, either alone or in conjunction with such other substances as are also capable of increasing the hydration capacity of the tissue colloids. Or, to repeat, *what we call the serious complications of nephritis are not really complications secondary to this pathological entity, but are manifestations in other organs of the body, of the thing which in the kidney we call nephritis.*

Just as the nephritis is in large measure an œdema of the

kidney, so the optic nerve swelling and the "retinitis" of nephritis are œdemas of the optic nerve and of the retina; the headache, convulsions, and coma are manifestations from an œdema of the brain, the persistent nausea and vomiting of central origin, manifestations from an œdema of the medulla; the generalized œdema, an expression in the body tissues of what in the kidney we call nephritis. The same intoxication or the same vascular disease, underlies all these changes, and it is a mere accident that one nephritic will show particularly prominent eye symptoms, another a great generalized œdema, while a third will call us to his side by a convulsion. For any one of a number of reasons, the œdema may become particularly prominent in his optic apparatus, or in his body tissues generally, or in his brain. If we bear these facts in mind, it will serve to indicate why I believe that any or all of these signs demand the same general treatment, and why, when we succeed in combating a particularly prominent one, we find that we have succeeded in combating all the rest as well.

Whether the particularly alarming symptoms spring from the kidney itself (a suppression or urine, a great albuminuria, etc.), or whether they spring from the brain (convulsions, stupor, coma), the eye ("papillitis," "retinitis," partial blindness), or the medulla (nausea and vomiting), the purpose of our therapy is the same—we wish to stop and reduce the swelling of the involved tissues.

Naturally the best and quickest way to do this is to inject something into the blood, and what this something must be we have already discussed.

Preparation of an Alkaline Hypertonic Salt Solution for Intravenous Injection

The following formula, already recommended above, does very well:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	10 grams
Sodium chlorid	14 grams
Distilled water, enough to make	1000 cc.

It is well to have this solution ready for immediate use, for its preparation in sterile form takes time, and need for it when it arises is urgent. What we have said regarding chemicals holds here also. Only chemically pure salts and *freshly distilled*

water are to be used. The crystallized sodium carbonate containing ten molecules of water of crystallization is recommended. If some other form of the salt is used, *less* than 10 grams to the liter are to be used, as discussed on page 681.

The finished solution as injected into the patient must be perfectly clear and sterile. Simple as it would seem to be to obtain this result, it is not always secured even when its preparation is left to trained helpers. Therefore, I may be pardoned for detailing the following rules for its preparation in containers that make it available for immediate use.

Trouble arises from the fact that alkaline solutions cannot long be kept in contact with ordinary glass containers without reacting with the glass and so leading to a separation of insoluble silicates. High-grade glass flasks resist better than other material, and so the finished solution may be sterilized and kept in these. For this purpose, it is only necessary to dissolve the sodium chlorid and the sodium carbonate in the necessary amount of freshly distilled water and filter the solution through moistened filter paper (in order to get no shreds into the solution) into the thoroughly cleaned flasks. It is convenient to have two liters of solution in each flask. The flasks are stoppered with gauze-wrapped cotton stoppers, and may be sterilized in the ordinary way by boiling. This scheme works well in hospitals or anywhere where storage room is plentiful.

When needed for injection, this solution may then be poured into any one of the properly sterilized intravenous injection apparatuses that abound in the market. If the solutions show a precipitate in spite of the use of good glass containers, the clear solution may be decanted or the whole may be filtered through a sterilized funnel into the neck of which has been forced a little sterile glass wool. Or a sterilized glass bulb insert of the type shown in Fig. 211, into which has been forced some glass wool may be used in the delivery tube of the injection apparatus. As the carbonates and hydroxids of the polyvalent metals are all insoluble, *every piece of any injection apparatus must be rinsed and sterilized only in distilled water.* When ordinary tap water is used calcium and magnesium precipitates cloud the injection mixture.

FIGURE 211.

In my own experience I have found it convenient to make

up the sodium chlorid-sodium carbonate solution in concentrated form in ampoules, and then mix this with enough freshly distilled water to yield the proper injection mixture at the time it is needed. One proceeds as follows:

Any desired number of multiples of 10 grams of sodium carbonate ($Na_2CO_3 \cdot 10H_2O$) and 14 grams of sodium chlorid are dissolved in enough water to make 60 cc. of finished solution. This solution is filtered and then sterilized by boiling.[1] One or more ampoules of the type shown in Fig. 212, *A*, and of about 60 cc. capacity (if these are not available, bottles will do as well) are thoroughly cleaned, rinsed in distilled water, and then boiled in distilled water to sterilize them. Into each of these is then filtered through a small sterilized funnel plugged with glass wool, 60 cc. of the concentrated sodium carbonate-sodium chlorid mixture. When the ampoules have been filled, they are sealed in a flame, as in Fig. 212. *B*. If bottles are used they are stoppered with sterile rubber or paraffined corks, and over these is fastened a sterilized paper hood to protect the necks from contamination. When an intravenous injection is to be given, an ampoule is taken, its neck is nicked with a file, and this and the lateral bead are cleaned with alcohol, and broken off. The contents are then poured into 940 cc. of freshly distilled water, *care being taken to mix the whole* so that the specifically heavier salt solution may not simply settle to the bottom.

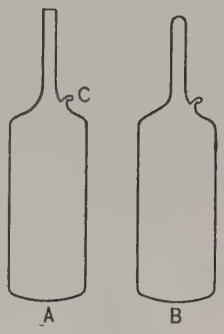


FIGURE 212.

After many trials I have found these the best ways to proceed, and as dispensing pharmacists in any community are willing to carry ampoules as here described in stock, one can easily obtain fresh and clean solutions at all times. If a precipitate of silicates should be found in an ampoule, one can readily avoid pouring this into the injection apparatus, or one may filter the contents of the ampoule through a little glass wool.

[1] In the first edition of Nephritis and in a paper or two I cautioned against the use of excessive heat in sterilizing these carbonate solutions. The caution I find was scarcely necessary, for at the ordinary temperatures and pressures at which such sterilization is carried out, the carbonate is not decomposed.

Technic of the Intravenous Injection of the Solution.

My experience has convinced me that it is best in making these intravenous injections to cut through the skin and expose clearly to view the vein to be used. The results are bad if one fails in his attempt to enter a vein with a hypodermic needle through the skin. The salt-alkali mixture produces a great destruction of the tissues if it is by accident injected into them. *Under no circumstances must such salt-alkali mixtures ever be given subcutaneously, under the breast, or intramuscularly.*[1]

A vein that is deemed sufficiently large is sought in the arm, in the leg, or, if necessary, in the neck. As we may wish to make several injections it is advisable to pick for the first injections the prominent veins *most distant* from the heart. Unfortunately in many of the conditions in which we wish to use the sodium chlorid-sodium carbonate solution, not much choice is allowed, for the blood vessels are so much contracted (toxemic shock?) that it is often impossible to find any usable vein below the bend of the elbow. Even here surgeons have been unable to find the median basilic in such cases. This will explain to the reader why in extreme cases such a vein as the jugular needs to be and has been used.

To expose the vein painlessly a few drops of a cocain or novocain solution may be injected into the skin. If the patient is stuporous or in coma this is, of course, needless. The vein is freed from its surroundings and a ligature is tied about its distal end. A second ligature is thrown about the vein and after a cut has been made into the vein and the cannula connected with the injecting apparatus has been inserted, this second ligature is tied. Of course, care is taken to have no air enter the vein.

The best type of cannula to use is shown in Fig. 213. The two openings at the tip and laterally make it well-nigh impossible to shut off the infusion stream by crowding the cannula against the vein wall. The tapering character of the cannula allows one to push it into even

FIGURE 213.

[1] Men who have failed to heed this oft-repeated caution of mine have been severest in attacking my teachings. Is it too much to ask critics at least to read what one has written?

a small-calibered vein, and the corrugation holds the cannula in place when the second ligature is tied.

Sometimes it is better to use a large hypodermic needle in place of the cannula. The first ligature about the exposed vein then serves to steady the vein when the needle is pushed into it. When the hypodermic needle is used it is simply held in place until the injection is completed. As can easily be imagined, the use of the needle is especially convenient when one works with such a vein as the jugular. The disadvantages in its use arise from the fact that one is likely at any time to injure the blood vessel if the patient moves, and from the further fact that the carbonate solution affects the coat of the vein and so tends to leak out about the needle after the injection has been kept up for some time.

The medical attendant should choose for intravenous injection the apparatus with which he is most familiar.

Perhaps that shown in Fig. 210, with a cannula replacing the catheter, and minus the thermometer and the insert *F*, is the simplest available form. The side tubulation with the rounded bottom, or a glass bulb insert filled with glass wool (Fig. 211) will make it almost impossible, if care is used, to inject any sediment that may accidentally appear in the injection fluid.

The pressure bottle arrangement shown in Fig. 214 possesses some advantages over the apparatus just referred to. No special comment is necessary regarding its use, and we need not in this day emphasize the necessity of having all rubber tubes, etc., perfectly sterilized by boiling in distilled water.

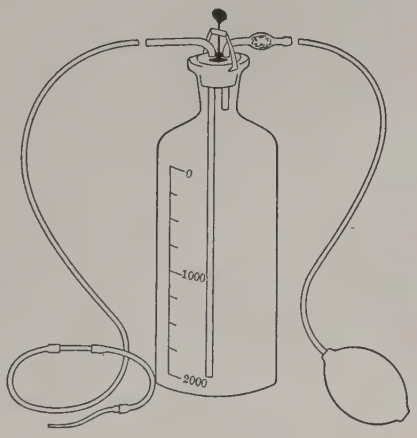


FIGURE 214.

The faults of the apparatus shown in Fig. 214 are that it possesses no arrangement for keeping the solution at body temperature, and that we do not know in as accurate a manner as we desire, the exact rate and the exact pressure at which the sodium

chlorid-sodium carbonate solution is entering the patient at any moment. To meet these difficulties, the useful apparatus shown in Fig. 215 was devised by Edmund M. Baehr. We have here again the glass pressure bottle shown in Fig. 214, but it is now surrounded by a copper water jacket by means of which the injected fluid may be kept at body temperature or a little above. The thermometer registers the temperature existing in the jacket, and as the temperature of the injection fluid falls on its way into the patient, it is advantageously kept a little above that at which we wish to deliver the solution into the patient. The rubber bulb in Fig. 214 is advantageously replaced in the apparatus shown in Fig. 215, by a metallic pump. A mercury manometer, inserted as indicated in the drawing, allows one to know at all times the exact pressure obtaining in the pressure bottle.

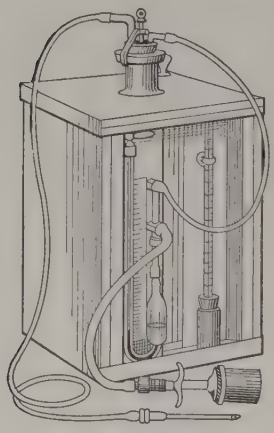


Figure 215.

One needs at all times to *inject the solution slowly* into the circulation so that it may mix with the blood, and at as even a rate as possible. Not over 30 to 40 cc. should be injected per minute. By testing out the apparatus before making the injection one can easily note just how much pressure is necessary to accomplish this. As the pressure in the larger veins is almost *nil*, 30 to 40 mm. of mercury pressure usually suffice, and one need never run above 50 mm. if a cannula or needle of proper diameter is chosen. If we give the solution to a patient who for any reason has to maintain an upright position, it is well to remember that in such a case the arm must be comfortably supported in as horizontal a position as possible in order not to have to work against a considerable hydrostatic pressure in the veins. The pressure and the oscillations of the mercury column tell us every moment whether our solution is flowing in properly or not.

The Quantity and Time Interval of the Salt-Alkali Injections

It is necessary to say now how much of the solution may be injected at one time and how often the injection may be repeated.

In any suppression case or in a case with convulsions, persistent vomiting or other alarming symptoms, 1800 to 2000 cc. of the solution should be given for the first dose. In the case of a child we give a proportionate dose obtained by dividing the child's weight by that of a small adult. A 30-kilo (66-pound) child gets half the dose of a 60-kilo (132-pound) man, etc. The repetition of the injection and the amount given subsequently must then be determined by the condition of the patient. If, within two or three hours, urine begins to come and the convulsions stop, or if the sensorium clears or the headache and eye symptoms improve, then we know that we have given enough for the time being.

If the patient is awake, he is likely to complain of thirst during the hour that we are making the injection. It is best not to let him satisfy this immediately, for we wish to get as great a shrinking effect of the salt and alkali upon his various organs as possible. But there is no objection to his moistening his mouth, and at the end of four to eight hours, if his alarming symptoms seem to be under control, we are only too glad to have him drink. Only we must always remember that as soon as water is given we decrease the patient's salt concentration, and if his kidneys are functioning, we are actively washing salt out of the body. So, to carry along our therapy, we give a natural or artificial alkaline water instead of plain water by mouth, and with this we may give various salts. By thus giving alkali and salts by mouth or by using alkali and salt by rectum, we may now be able to keep our patient growing progressively better. But if this is not the case, or if the redevelopment of some prominent sign or symptom informs us that our patient is relapsing into his previous state, then we may give a second injection of one or even two liters of solution, six, twelve, or twenty-four hours after the first injection. Closer rules than this can hardly be given. If our patient improves for a number of hours after the first injection, and then goes down again, we repeat the injection at this time; 500 to 1500 cc. in any twenty-four hours after the first injection is certainly safe.

If the suppression of urine is not absolute, then it is a useful guide to the amount of alkali and salt that may be urged upon the patient. *It is safe to give alkali and it should be given until the urine is persistently neutral to litmus.* For self-evident reasons, it is possible for the urine to be alkaline immediately after

an intravenous injection, even when the acid content of the body generally is still abnormally high. Not until the urine is *persistently* neutral and is held there are we really succeeding in getting an adequate amount of alkali into the patient.

Various observers have commented on the large quantity of fluid that is injected intravenously in clinical cases of nephritis and allied conditions. I have injected as high as 6 liters (6 quarts) in twenty-four hours. Some clinicians have for various reasons remonstrated that this is dangerous, chiefly because they hold such injections to "increase the blood pressure." Observation is better than guessing in settling such points. Measurement made just before and just after a two-liter intravenous injection shows either no change whatsoever in the blood pressure, or, if it has previously been high, a fall.[1] Others hold such injections to "throw work on the heart." In so far as the elimination of water from the body costs energy, this is to a limited extent true, but only to a very limited extent, as I have previously insisted. Physiologists know that the volume of the circulating blood can be more than doubled without appreciable effect. Counting the blood in the human being as one-thirteenth the body-weight, it is therefore entirely safe to inject a liter of fluid for every 13 kg. (about 28½ pounds) of body-weight; but as pointed out previously, this is a safe figure if blood, in other words, water in combination with a colloid, is injected. Only such remains in the blood vessels. When the water is injected "free," as in a salt solution, this rapidly leaves the blood vessels, and so the amount of this that may safely be injected lies still higher. What I have said here is still largely true even when we deal with sclerosed blood vessels, though to allow for the diminished elasticity, a slower injection or injection of a less amount at more frequent intervals, as the judgment of the operator may dictate, may advantageously replace the single large injections.

About one in every three patients injected with alkaline hypertonic salt solution develops some reaction. At times he develops a chill which, however, does not last long, or he has a slight rise in temperature.[2] Once I found sugar in the urine.

[1] James J. Hogan: Lancet-Clinic, **113**, 6 (1915).

[2] See in this connection Rollin T. Woodyatt, J. O. Balcar and W. D. Sansum: Arch Int. Med., **24**, 116 (1919).

It will be noticed that these findings are similar to those observed after intravenous injections of salvarsan and other medicaments. European authors have laid stress on the distilled water employed in making up the solution, maintaining that bacterial products are present in old distilled water. For this reason I have always urged the use of freshly distilled water, but even then I have seen these reactions. I next attributed the effect to the action of the alkali on the red blood corpuscles, and a resulting hemolysis. This, however, can only be a small part of it, for one of the worst reactions I ever saw occurred in a woman to whom I gave a concentrated solution of neutral salt only. To explain the findings I have come to the tentative conclusion that two things are active: first, a shrinking of the red blood corpuscles which makes these less able to carry oxygen; second, a more important direct action of the salt and alkali on the medulla. The latter effect I think, leads to the vasomotor disturbance in the skin which we call a chill, to the consequent retention of heat that accounts for the rise in temperature, and to the appearance of sugar in the urine, as C. Bock and F. A. Hoffmann [1] found many years ago when rabbits were perfused with sodium chlorid solutions. How to avoid these effects is not yet entirely clear. The rules I have formulated for my own guidance call for the use of freshly distilled water and as slow an injection as is conveniently possible. It is undoubtedly better to give in place of single large intravenous injections several smaller ones separated by intervals of time which allow the salt and alkali to diffuse into the body-tissues, but unfortunately the necessity of opening into more than one vein and the critical condition which we are usually asked to meet does not always allow of this. Before, throughout and after the injection the patient is carefully protected from muscular exertion, and the possibility of a chill is guarded against by extra blankets, hot-water bags, etc. If complete muscular and mental relaxation is not easily obtained, a *small* dose of codein, heroin or morphin may be used.

Perhaps the way to proceed is best illustrated by abstracting a few clinical experiences and commenting upon them directly.

[1] C. Bock and F. A. Hoffmann: Arch. f. (Anat. u.) Physiol. (1871). Martin H. Fischer: Univ. of California Publications in Physiology, **1**, 77 (1903); **1**, 87 (1904); Pflüger's Arch., **106**, 80 (1904); **109**, 1 (1905).

7. Clinical Abstracts and Comment

§ 1

The credit of having been the first to utilize upon patients the principles outlined in this volume belongs to James J. Hogan. Since then others of my friends and colleagues have used alkalies, salts, and water for the relief particularly of the acuter nephritides, and their accompanying manifestations, and with favorable results. My thanks are due them all for permitting me not only to see many of their patients with them but to use the facts contained in the brief illustrative histories that follow.

Case VII.—Mr. G. B., a laborer, aged twenty-four years, and previously in good general health, was operated upon under ether at 9 p.m., February 15, 1912, for a right inguinal hernia of several years' standing. The operation was a long one. Examination of the urine before operation had been negative. Nothing abnormal was noted except that vomiting was rather severe after the operation, continuing until late in the afternoon. At this time, in response to inquiry the patient said he had no desire to urinate. The same condition existed late that night, even though by this time the patient was swallowing and retaining considerable quantities of water. The following morning the patient was catheterized, and 20 cc. of brownish, viscid liquid heavily charged with albumin were obtained. Through the day he was given hot drinks and hot fomentations over the kidneys, but no spontaneous voiding occurred. At 9 p.m., that is to say, eighteen hours after the operation, he was again catheterized, and 15 cc. of urine of the previously described character were found. At this time liquid by mouth was stopped and administration of the following solution by slow drip into the rectum was started:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	10 grams
Sodium chlorid	14 grams
Distilled water, enough to make	1000 cc.

The patient retained the solution well, and by 10.30 had taken up the whole liter. At 11.45 he asked for a urinal, and passed 180 cc. of highly albuminous urine filled with casts and red blood cells. At 1 a.m. he passed another 160 cc., and at 3 a.m. 205 cc. The urine by this time was almost as clear as water.

As he felt thirsty, a glass of water was now permitted him every hour. The urinary output continued so that by 9 p.m. of February 16, that is to say, in the first twenty-four hours after the drip was started, 2350 cc. were voided. By the evening of this day the albumin had dwindled to a trace, and only occasional granular casts could be found.

In the following two days, during which 2470 and 2385 cc. respectively of urine were obtained, these signs disappeared entirely. The urine of this patient, who is entirely well, has been examined repeatedly since, with negative results.

Case VIII.—Mrs. M. L. T., aged forty-seven years, a laundress, was operated upon under ether for an extensively broken pelvic floor with prolapse of the uterus, at 8.30 A.M., July 1, 1912. She had not been in good general health previously, though she complained of nothing specifically excepted her uterine condition. Urinary examination on admittance to the hospital the day previously had shown a trace of albumin and occasional casts, but the general condition of the patient did not seem sufficiently bad to contraindicate an operation which was much needed. Her condition after the operation was fair, but she did not urinate. Catheterization twelve, twenty, and twenty-eight hours after her return from the operating room was dry. At 9 P.M., July 2, when catheterization was again found to be dry, she was slowly injected intravenously with 1600 cc. of the following mixture:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	20 grams
Sodium chlorid	28 grams
Distilled water enough to make	2000 cc.

She was catheterized at 3 A.M., when 90 cc. of a viscid, brownish urine, filled with albumin and casts, were obtained. The urine was highly acid to methyl red.[1] At 7 A.M. another 90 cc. of a similar looking urine were obtained. Because of the perineal operation, rectal injection of alkali and salt was not urged, but half a glass of Vichy water, with a powder of half a gram each of sodium bicarbonate and magnesium oxid, was given every hour. On this régime 420 cc. in all of brownish, highly albuminous urine filled with casts were obtained in the first twenty-four hours after the intravenous injection. This alkali therapy was continued. The urine became neutral to litmus and remained so after July 5. In her second twenty-four hour period she secreted 670 cc. of urine, and in the third, 1140. The urine became clearer, the casts fewer, and the albumin content diminished steadily (from 9 grams to the liter in the first specimens to 1.5 grams on July 5 and 6). Her further history is summarized below:

For 24-hour period of	Amount of urine.	Grams of albumin per liter (Esbach).
July 7	1790	1.0
July 8	2100	0.8
July 9	1873	0.9
July 10	1840	0.5

[1] The advantages of using methyl red and paranitrophenol as indicators instead of the ordinary litmus are explained on page 774.

Numerous hyaline and granular casts were found in all these specimens. These continued with a urinary output of 1700 to 2200 cc. per twenty-four hours, containing albumin that varied little from half a gram per liter until she was discharged from the hospital July 21.

A more detailed physical examination after her operation than had previously been possible, showed this patient to have easily palpable peripheral blood vessels with an evidently enlarged but regularly beating heart. The systolic blood pressure was 165 mm. of mercury, the diastolic 140. Tender bones with bogginess of the tibial periosteum, a tender nasal bridge, vague night pains, and three miscarriages for which no cause was assigned, together with the casts and albumin found on admission to the hospital, led to the diagnosis of syphilitic vascular disease with cardiac hypertrophy and involvement of the kidney (chronic interstitial nephritis).

Since leaving the hospital this patient has been seen occasionally. Some albumin and casts are constantly found in the urine, and her blood pressure continues at approximately 160 mm. The patient herself complains of nothing and feels herself improved by her operation.

In the light of our considerations it is not surprising that an anesthesia nephritis as illustrated in these two cases is easily relieved by alkali and salt. During an anesthesia we introduce into the body a poison which interferes with the normal oxidation chemistry of the cells and that we have an abnormal production and accumulation of acid following this, is attested not only by the thirst of which the patient complains, but by the accelerated breathing and heart beat, the abnormally high acid (hydrogen ion) content of post-anesthetic urine, and the appearance in it of such "acidosis" products as acetone, diacetic acid, lactic acid, etc. But as soon as we stop administering the anesthetic the patient begins to exhale it, and so in a comparatively short time the intoxication responsible for the abnormal production and accumulation of acid disappears.

The patient also usually succeeds in oxidizing the acid products resulting from his intoxication, and so it is the usual thing to see him bear his anesthesia without bad after-effects. But sometimes he is not so successful and then if his intoxication evidences itself chiefly from the side of his kidneys, we say he has a postoperative nephritis. (If it should happen to involve his liver particularly, we say he has a "postoperative jaundice," a "chloroform liver," etc.). There is nothing surprising about the fact that an administration of alkali and salt relieves this condition. The alkali neutralizes the abnormal acids present, and the

increased salt concentration reduces the hydration capacity of his swollen kidney (and other body) colloids. If the injury to them has not been too great (or technically put, if the colloid changes characteristic of nephritis have not become "irreversible"), these measures quickly restore his kidneys (and other involved organs) to a more normal state. As the kidney shrinks, a better blood supply to the organ is obtained, and so the kidney cells are once more enabled to resume their work. Once this result has been obtained a recurrence need scarcely be feared, for the original intoxicant (the anesthetic) has by this time disappeared from the body, and so the relief obtained is permanent.

What has just been said applies in my judgment to Case VII. In Case VIII the problem is essentially the same, only the anesthesia intoxication is this time added to the effects of a blood-vessel disease which in itself has already led to the signs of a nephritis. The effects of the anesthesia intoxication could, as in Case VII, be overcome, but an injection of salt and alkali does not remove an endomesarteritis with its effects upon parts or all of the kidney, and so casts, albumin, etc., continue to be found in the urine even after the suppression following the anesthesia has been relieved.

§ 2

If we will write the name of any other intoxicant in the place of anesthetic in these considerations, we have what happens, to my mind, in the nephritides that we encounter in any of the acute infections, and in the various other acute intoxications which we know to be associated with the development of nephritis. Here again nature herself takes care of the great majority of cases, but when she does not, we may again be able to relieve the urinary condition by alkali, salts, and water. Such a situation is illustrated in Case IX, where an unknown intoxicant led to suppression of urine and in cases X and XI, where the suppression followed scarlet fever.

Case IX.—(Dr. Elizabeth Campbell, Cincinnati, Ohio.) A. H., a girl, aged three and one-half years, had never been ill previously. When first seen she was extremely nauseated and vomiting. There was a slight general œdema, and her urinary output was low. The urine contained much albumin and casts. Enemas of 0.85 per cent sodium chlorid solution and calomel by mouth improved the child's condition, and brought up the urinary output. Five days later the

mother reported that since two in the afternoon of the day before the child had passed no urine. The child was given hot baths and sweated several times. Several 0.3 gram doses of sodium bicarbonate were given by mouth, and water was urged. The child had vomited once. She was extremely quiet. Temperature and respiration were normal. The pulse was 76. 0.2 gram calomel was given at night, and through the night hot alkaline drinks, blanket sweats, and enemas of 0.85 per cent sodium chlorid solution were continued. The anuria persisted. This scheme of treatment was kept up through the following day also. The general œdema had in the meantime increased, the patient was vomiting, and had grown stuporous, and the pupils reacted slowly. In consultation in the early evening of this the third day of the anuria it was decided to try the administration of an alkaline hypertonic sodium chlorid solution. As it was thought there might be some urine in the bladder, the child was catheterized. A teaspoonful of bloody urine was obtained. At 9 P.M. 320 cc. of the following solution were injected into the rectum by slow drip, the child retaining all of it.

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	15 grams
Sodium chlorid	14 grams
Water, enough to make	1000 cc.

The child had a restless night. At 5 A.M. she passed 96 cc. of urine that looked like pure blood. This was sixty-three hours after the suppression was first noted. At 6.15 A.M. another 130 cc. of bloody urine were passed; at 7.30, 256 cc., with only a slight amount of blood. At 10 A.M. a large voiding was lost with a watery stool. An hour later 250 cc. of the above alkaline hypertonic sodium chlorid solution were slowly injected into the rectum. Through the afternoon the nurse reported that "the urine came in an almost steady stream." The albumin content of the urine fell rapidly, so that by the following day only a trace could be found, and on the fourth day later it disappeared entirely. The general œdema disappeared rapidly, and was about gone on the third day after the urinary secretion became reestablished. Recovery has been complete.

Case X.—(Dr. James J. Hogan, San Francisco, California. Mrs. W., twenty-two years old, had passed through a scarlet fever. Dr. Hogan was called in consultation on the evening of March 11, 1911, and found the patient unconscious with practically a complete suppression of urine that had lasted for twenty-four hours. The unconsciousness had lasted for twelve. The following formula was given by the continuous drip method into the rectum:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	20 grams
Sodium chlorid	14 grams
Distilled water, enough to make	1000 cc.

The urinary flow recommenced after four hours; on the following day her mind had cleared, and the patient made a subsequent uneventful recovery.

Case XI.—(Dr. H. Kennon Dunham, Cincinnati, Ohio.) Master M., seven years old, was seen on April 30, 1911, by Dr. Wm. C. Schmidter in a rather mild attack of scarlet fever. The temperature at no time ran above 101° F. In spite of the apparent mildness of the attack, the child developed urinary symptoms. On May 7, when Dr. Dunham was first summoned in consultation, a complete suppression of urine had lasted for fifty-one hours, the child was conscious, but very stupid, presenting a grave picture of intoxication. The eyelids and ankles were swollen, the pulse 105, respiration 24.

At 4.00 A.M. the following mixture was prepared and its injection into the rectum begun:

Sodium carbonate ($Na_2O_3 \cdot 10H_2O$)	20 grams
Sodium chlorid	30 grams
Distilled water enough to make	1000 cc.

The injection required one and a half hours. About 180 cc. were rejected, the remainder of the above solution was retained. Three and a half hours after the injection was completed the patient passed involuntarily a large watery stool. Ten hours after the completion of the injection he passed a small amount of highly colored urine. Following this at short intervals came large voidings of urine which were lost into the bed, as the child could not control himself sufficiently to use a bedpan. Not until this secretion had lasted for four hours could the urine be collected. Not counting that which was lost there were collected 2272 cc. of urine in the first twenty-four hours after urinary secretion commenced. The first specimens of urine obtained were so filled with albumin as to set into a solid mass on boiling. The amount of albumin rapidly decreased, so that during the second day after the injection only a moderate reaction for albumin was obtained, and on the ninth day it disappeared entirely. The intense stupor left the child within the first twenty-four hours after injection, and on the third day he was actively interested in his surroundings and free from œdema. His urinary secretion after being started was readily maintained by the milk diet on which he had been from the first and to which alkaline mineral water was added *ad libitum*.

§ 3

For self-evident reasons our prognosis grows worse and our efforts need to be greater as the intoxication grows in length or becomes of a less removable type. We encounter this situation in protracted infections, in acute infections that leave behind toxins that stick particularly firmly to the kidney cells (scarlet fever?) and in poisonings of this type (phosphorus and the metals). Not alone do some of these produce irreversible colloid changes (necrosis) in the cells of the kidney from the start—changes, therefore, which can never be "cured" by any thera-

peutic procedure—but even when such is not the case, in these lasting intoxications the interference with the normal oxidation chemistry of the kidney cells is of a more lasting character, and so our therapy must also be more persistent. A single dose of alkali and salt may then do no more than give temporary relief. We must meet the intoxication as long as it persists.

Cases XII, XIII, and XIV may serve in illustration of these remarks.

Case XII.—(Drs. Otto P. Geier and J. L. Tuechter, Cincinnati.) G. L., a 34-year-old attorney, developed a severe tonsillitis involving both tonsils on May 17, 1911. His temperature was 103.5° F., pulse 120. The urine was very scanty, highly colored, and contained albumin and casts. The next day the patient had intense headache, and in the evening became delirious. During these second twenty-four hours of his illness he passed but 90 cc. of urine, very smoky in color and filled with albumin, red and white corpuscles and casts of all sorts. On the third day of his illness he passed no urine at all. His delirium continued and his temperature remained at 103° F., his pulse at 124. Late at night he was given the following mixture per rectum:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	20 grams
Sodium chlorid	14 grams
Distilled water, enough to make	1000 cc.

In his delirium most of the first injection was rejected. At 3.00 A.M., May 20, the injection was therefore repeated. About 500 cc. were retained. At 6.00 A.M. 150 cc. of dark, thick urine were obtained which on heating fairly set into a jelly. The urinary secretion became more profuse as the day wore on, and in the first twenty-four hours after the successful injection 1184 cc. of urine were obtained. As the urinary secretion increased, the drowsy delirium passed away, the headache disappeared, and the patient volunteered that he felt well. The temperature fell to 101° F., the pulse rate to 100. The later specimens of urine voided in these twenty-four hours after the successful injection were clear and amber in color and contained only a little albumin, and few casts and blood cells. The rectal injections of 500 cc. of the above formula were repeated May 21 (temperature 99.5° F., pulse 90) and May 22 (temperature normal, pulse 70). Between the injections the patient was urged to take as much Vichy water by mouth as he could. The urine secreted May 21 measured 1376 cc., that secreted May 22, 1408 cc. Some albumin and casts were found in the former, only a trace together with some red blood corpuscles but no casts in the latter. On May 23 all urinary signs had disappeared, and the patient made an uneventful recovery.

Case XIII.—(Dr. William E. Kiely, Cincinnati.) Three weeks before entering the hospital S. C. W., thirty-eight years old, and a mod-

erate beer drinker, became short of breath, suffered from headaches, and noticed a swelling of his legs and abdomen. Physical examination showed no disease of the heart or lungs, but fluid in the pleural and peritoneal cavities, with a general œdema of the subcutaneous tissues. The urine was low in amount, of high specific gravity, and contained much albumin, some blood cells, and hyaline casts. On this a diagnosis of (*chronic*) *parenchymatous nephritis* was made. After twenty-five days of rest in bed, a milk diet, a daily hot bath, saline cathartics and digitalis, no improvement in his general condition was noted. There was now added to his diet a liter of water daily containing 25 grams of sodium chlorid. Improvement in his general signs and symptoms began immediately, the urinary output rose, the blood disappeared, and the casts and albumin progressively diminished in amount. After ten days of this treatment he was much better, and at the end of twenty-five all signs of his œdema and the effusions into his serous cavities had disappeared. At his own request he got out of bed and began to work about the ward, and shortly thereafter left the hospital free of all signs and symptoms, except a faint trace of albumin in his urine. In this state he has continued up to the present time (that is, for two months since leaving the hospital).

Case XIV.—(Dr. Julius H. Eichberg, Cincinnati.) A. B., a 40-year-old lawyer, entered the hospital in April, 1911, with a history of kidney disease of eight years' standing. At various times during these years he had had a diagnosis of *chronic parenchymatous nephritis* made upon him. He had no enlargement of the heart and no increased blood pressure. The original cause of the nephritis could not be made out. When first seen the patient was passing about 400 cc. of urine per twenty-four hours, containing 4 grams of albumin per liter and filled with all varieties of casts. On a milk and vegetable diet, sweat baths, and saline cathartics his urinary secretion increased somewhat, but his general condition did not improve, the number of grams of albumin lost each twenty-four hours did not decrease, and his œdema, ascites etc., increased. After two weeks in the hospital he had a well-marked œdema of his legs, back, chest-wall, scalp, and face. The fluid in his abdomen extended to the umbilicus when sitting up. While his general hospital régime and diet were kept as before, he now had added to his drinking water and consumed each twenty-four hours 7 grams of dried sodium carbonate. After ten days of the carbonate administration his œdema and ascites disappeared completely, his urine increased to approximately 800 cc. per twenty-four hours, though the quantity of albumin lost per twenty-four hours did not change perceptibly.

The patient at this point refused to continue taking the carbonate. In five days his weight went up $2\frac{1}{2}$ kilos. The patient was persuaded to resume the carbonate, and at the end of another seven days his original weight had again been attained, and the visible signs of œdema which had developed when the carbonate was discontinued had once more disappeared. The urinary output amounted at this time to 800 cc. daily, and the albumin dropped to 2.5 grams per liter.

At this point the patient refused a second time to take the sodium carbonate, and again the swelling of his legs and back developed, while his weight rose as before, 2½ kilos in less than a week. Following this period he returned a third time to the carbonate, and in six days had again lost his 2½ kilos and the obvious signs of an œdema. This is his state at the present writing when for four months he has been passing 1280 cc. or more of urine daily, containing some casts and 0.75 gram of albumin per liter. He has left the hospital in fair condition, has a good appetite, sleeps well, and has resumed the practice of his profession.

§ 4

The nephritides occurring in the course of pregnancy [1] constitute a common and important group. How alkali, salt and water help in their management is illustrated in Cases XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, and XXIV.

[1] The origin and nature of the poison which gives rise to the symptoms of the pregnancy intoxications form interesting food for speculation. The beginning of the intoxication with pregnancy and its prompt cessation with birth of the child, together with the fact that an organism is immune to its own proteins, makes me believe that the foreign protein of the male brought in with the spermatozoan marks the starting point of the intoxication. In this sense the morning sickness, the nausea, etc., occurring early in the pregnancy mark the beginning of the intoxication, but as immunity is usually established they are likely to pass away. When immunity is not established the severer signs of the later months of pregnancy supervene. A woman who has once been pregnant is less likely to be a second time the victim of an intoxication, because the immunity developed in a first pregnancy protects her against the intoxication consequences of a second. Moreover, a woman married more than once may show intoxication with one and not with another man (because the foreign protein is different in the two). Termination of the pregnancy (removal of the foreign protein as contained in the developing embryo) cuts short the intoxication. Many circumstances, moreover, serve to aggravate the nephritis encountered in pregnancy when it has once become established. Such are the "acidosis," for example, secondary to the starvation consequent upon the vomiting, the nausea, and the absurd dietary restrictions to which these patients are so often subjected, a state betrayed only too clearly by the high ammonia excretion and the presence of acetone, diacetic acid, etc., in the urine.

I should further like to emphasize that not every nephritis observed in a pregnant woman is at once to be attributed to the pregnancy, as is so generally done. Vascular disease and infections of the kidney are very commonly overlooked. It has also been my experience that many patients are said to have a pregnancy intoxication resulting in the death of the fetus when as a matter of fact syphilis or some other condition first killed the fetus and the products of its decomposition then served to affect the kidney.

Case XV.—(Dr. James J. Hogan, San Francisco, California.) Mrs. R., pregnant and practically at term, entered the hospital March 7, 1911, at 5.30 p.m., complaining of continuous uterine pain. She had a general œdema. Signs and symptoms indicating that a nephritis had existed for at least some days past were evident, but no proper examination of the urine had been made. The os on examination was found rigid. Because of the intense pain 0.015 gram morphin was given hypodermically at 9.00 p.m. She went to sleep but awoke at 11.00 in a severe convulsion. The patient was catheterized and 60 cc. of bloody urine of a syrupy consistency were obtained. On testing this for albumin it fairly set. Casts, cellular detritus, red blood cells, etc., were found microscopically. 600 cc. of an 0.85 per cent sodium chlorid solution were given by rectum and immediate emptying of the uterus was deemed necessary. This was done under ether anethesia and as the os was very rigid required a half hour. A second convulsion occurred on the operating table. Immediately after the operation another 500 cc. of an 0.85 per cent sodium chlorid solution were given by rectum. Between this time (11.30 p.m., March 7) and 4.50 p.m., March 11, in other words, for practically four days, no urine could be obtained by catheter. During this time no convulsions occurred and the patient's mind remained clear. A continuous salt drip was used in the rectum and water and magnesium sulphate were given by mouth, but no evidence of a return of urinary function was obtainable. It was now decided to use a more concentrated sodium chlorid solution and alkali. The following mixture was therefore prepared:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	20 grams
Sodium chlorid	14 grams
Water, enough to make	1000 cc.

This was injected into the rectum at body temperature by a continuous drip method. In an hour and ten minutes 30 cc. of bloody urine were obtained, and an hour later 80 cc. more. From now on the urine fairly streamed out. The secretion continued and the albumin and casts entirely disappeared from the urine by the fourth day. The patient made an uninterrupted recovery.

Case XVI.—(Dr. Lemuel P. Adams, Oakland, California.) Mrs. E., twenty-six years old and a primipara, began to feel below par, became pale, and developed a generalized œdema when pregnant seven and a half months. The secretion of urine was low, and this contained much albumin and various casts. Her condition gradually grew worse, so that it was deemed wise to put her to bed in the hospital. For ten days here, on a milk diet, and cared for in the approved ways, she showed no improvement, passing between 240 and 360 cc. of urine per twenty-four hours, filled with albumin, casts, and red and white blood corpuscles. As she now began to develop twitchings, was extremely œdematous and nearly blind, and as the onset of convulsions was feared, premature labor (at 8 months) was induced through gradual dilatation of the uterine os by means of water bags. Complete suppression of

urine followed delivery. After this had lasted for thirty-one hours and no urine had come consequent upon hot packs, cupping, digitalis, etc., a slow injection of the following mixture into the rectum was begun:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	20 grams
Sodium chlorid	14 grams
Water, enough to make	1000 cc.

Urine began to come four hours after the injection was commenced and amounted to 1536 cc. in the first twenty-four hours. Two injections daily of 500 cc. each of the above formula were continued for three days, together with water, milk, and cereals by mouth. On the second day 2176 cc. of urine were obtained, on the third 2140, on the fourth 2180, and on the fifth 1856. On the fifth day casts and blood cells had entirely disappeared from the urine and only the faintest trace of albumin remained. The œdema had diminished greatly, eyesight was returning, and the patient was actively interested in her surroundings. On the following day the last of the albumin was gone and the patient went on to an uneventful recovery.

Case XVII.—(Dr. Dudley Smith, Oakland, California.) Mrs. W., aged thirty, and seven months pregnant, presented herself for examination in May, 1911, with a history of nephritis and threatened eclampsia in her first pregnancy, ten years before. The second pregnancy, three years before, had been uneventful. Urinary examination when the patient first presented herself was negative. On June 7, she began to show albumin in her urine and marked signs of general intoxication. Œdema of the face and feet developed. She was put to bed and placed on a milk diet, and saline cathartics were administered. Under this treatment she got no better. About the first of July, active administration of alkalies was begun in the form of 1 to $1\frac{1}{2}$ grams of sodium carbonate dissolved in a glass of plain water, or Vichy water, every two hours. Marked and positive improvement occurred in all her general symptoms and the œdema disappeared entirely. She was permitted to get out of bed again, but the alkali therapy was continued. On this régime she was carried to full term with no further general symptoms of consequence. Her urinary output lay between 1800 and 2800 cc. daily and some albumin and casts continued in the urine. On July 24 she complained of severe continuous uterine pain, and with this came a marked reduction in the urinary output, extreme nervousness, and severe headache with nausea and vomiting. On the morning of July 25 the urinary secretion had stopped entirely. She was sent to the hospital at noon and the following formula was slowly injected into the rectum:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	15 grams
Sodium chlorid	14 grams
Water, enough to make	1000 cc.

At 3 P.M. the uterine pain, the headache, and the nausea had disappeared and the patient went to sleep. At 4 P.M. the rectal

infusion was given a second time and almost a liter was absorbed. At 11 P.M., 258 cc. of urine were voided and the patient passed a good night, sleeping soundly. The following morning 500 cc. of urine, very high in albumin, casts, and blood, were passed. At three o'clock of this day, she again developed severe headache, nausea, and vomiting, and was unable to retain the rectal infusions, or anything by mouth. At 10 P. M. all the symptoms had so increased in severity, that 300 cc. of the above solution were given intravenously. In fifteen minutes the patient volunteered the information that her headache and nausea were gone. She was comfortable until the next afternoon, when periodic uterine pains developed, and the headache and vomiting returned. The patient was taken to the operating room, and the cervix was dilated slowly by hand. Delivery of the living child was accomplished in an hour and a half. This was followed by another intravenous injection of 645 cc. of a solution containing $7\frac{1}{2}$ grams sodium carbonate ($Na_2CO_3 \cdot 10H_2O$) and 14 grams sodium chlorid to the liter. In the following twenty-four hours 2200 cc. of urine were voided, and as the nausea, vomiting, etc., had disappeared it was an easy matter to maintain such a urinary output by giving water and alkalies by mouth. Albumin and casts disappeared from the urine on the fourth day and the patient had an uneventful convalescence.

CASE XVIII.—(Dr. W. A. CLARK, Oakland, California.) Mrs. C. H., aged thirty-five, and pregnant for the second time, presented herself for examination in March, 1911. She had menstruated slightly, and for the last time, January 22. A year previously she had given birth to a healthy child at term, though in the later months of her pregnancy her limbs and face had swelled, she had much headache, and her eyes had troubled her. At the time of her first visit, and repeatedly afterward, physical examination and examination of the urine showed nothing abnormal. On August 11, she showed a well-marked generalized œdema, and complained of headache, extreme restlessness, sleeplessness, dimness of vision, and constant nausea. Her urinary secretion had fallen to 500 cc. per twenty-four hours, was highly acid, and high in albumin and casts. She was immediately sent to the hospital and kept in bed on a diet rich in water, alkalies, vegetables, and milk. Epsom salts were administered by mouth, and 0.85 per cent sodium chlorid solution was repeatedly injected slowly into the rectum. On this régime all of her symptoms and signs, including the albumin and casts, disappeared, and the urinary output rose, so that 2200 to 2674 cc. were voided every twenty-four hours. August 26 the patient felt so well that she insisted on getting out of bed and busying herself about her room. On the second day following this renewed activity, her headaches again showed themselves, and her nervousness and sleeplessness returned. On August 29 her nausea and vomiting became severe, and her vision very dim. The œdema of the legs and face returned, and her urinary output fell slightly, to 1984 cc. When the heat test was applied to the urine, the whole became solid. This condition continued

until 11.30 P.M. of August 30, when the headache, nausea, vomiting, etc., were so severe that it was decided to give alkali and salt intravenously. The following formula was given:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	10 grams
Sodium chlorid	14 grams
Water, enough to make	1000 cc.

In an hour the patient volunteered the information that her headache and nausea were better, and that she felt brighter. She slept well, and passed the next morning comfortably. Examination of the urine passed in the night and early morning showed a decided drop in the amount of albumin excreted. Even though the subjective symptoms of the patient continued well, the albumin content of the urine again rose so that on the morning of September 1 this was sufficient to make the contents of the test-tube again set in a solid mass when boiled. The amount of urine obtained continued good, being 1984 and 2048 cc. respectively, for the last two twenty-four-hour periods. It was deemed best to empty the uterus, and at 10 A.M. of September 1, dilatation of the uterine os by means of rubber bags was begun. Rhythmic pains began two hours later and as these increased in number and severity, the patient's headache and nausea increased, and the urinary secretion fell. At 4 P.M. the patient vomited and developed a twitching of the face and arms. This continued at intervals until 11 P.M. when two liters of the alkali-salt mixture of the composition previously used in this case, were injected intravenously. Shortly after this, the subjective symptoms of the patient became better and she fell asleep, passing a fairly good night, and examination of the urine again showed a decided drop in the amount of albumin present. The general condition of the patient continued good, and on the evening of September 2, she was delivered under chloroform anesthesia of a 1750-gram, living, female child (left shoulder presentation with version). On the operating table the patient received 1000 cc. of 0.85 per cent sodium chlorid solution under the skin, and for subsequent treatment the patient was given this same salt solution by rectum. Alkaline water (a gram of sodium carbonate in a glass of water every hour) was given by mouth. The urinary secretion on this régime never fell below 2200 cc. On September 4 the albumin in the urine had dwindled to a trace, and on the next day it disappeared entirely. Examination of the urine twice daily from this time on invariably showed an alkaline reaction to litmus paper and no albumin. The general œdema disappeared on the third day after delivery. On September 17 the patient was fully convalescent.

CASE XIX.—(Dr. N. A. HAMILTON, Franklin, Ohio.) Mrs. C., twenty-seven years old, and a primipara in the seventh month, showed nothing abnormal on examination, September 8. On September 20 some albumin was found in the urine, and on September 27 it was present in abundance. Her general condition was good.

At 10 P.M., October 2, she was seized with sudden nausea and vomiting which continued through the night. At 3.30 A.M., October

3, she had short lapses of consciousness. Headache was severe; there was some œdema of the face and legs; the pulse was 100 and hard. Veratrum was given by hypodermic injection. At 8.30 A.M. her pulse had fallen to 52; her temperature was normal. No urine had been passed through the night, but at this time she passed 30 cc. The patient was dizzy, still vomiting, had pain in her neck, and her sight was blurred. She was now given 800 cc. of a strong (hypertonic) sodium chlorid solution (1.5 per cent) by rectum. This was all retained. At 11.30 A.M. 90 cc. of dark-colored urine filled with casts and containing so much albumin that on boiling it fairly set was passed. Another 800 cc. of the sodium chlorid solution were now given and at 2 P.M. an unknown amount of urine was lost with a stool. Twenty minutes later a convulsion lasting a minute occurred, and this was repeated a half hour later. The patient was vomiting, and could not distinguish colors. There was a general twitching of the muscles. A general anesthetic was given at 3.30 and an attempt made to dilate the very rigid uterine os instrumentally. At 5.00 P.M. the membranes ruptured, and at the same time 30 cc. of dark-brown urine were obtained by catheter. At 6 P.M. the temperature of the patient was 100.2° F. by axilla. Another injection of 800 cc. of the strong saline solution was given by rectum at this time and repeated at 8 P.M., but neither was retained well. At 10 P.M. a little urine (estimated as 30 cc.) was passed with a stool. At midnight the patient's temperature was 100.2° F., she was dizzy, could not distinguish between men and women, and was unable to differentiate white from black. At this time she was given the following formula intravenously:

Sodium carbonate (crystallized)	20 grams
Sodium chlorid	28 grams
Water, enough to make	2000 cc.

The injection required an hour. While giving the injection the patient volunteered the information that her nausea had left her, and that her headache was disappearing. At 2.30 A.M., October 4, she passed 75 cc. of dark-brown urine filled with casts and fairly solid with albumin on boiling. At 4 A.M. she passed another 75 cc. and at 6.45 A.M. 95 cc. During these hours she slept at intervals. When she awakened her headache and nausea were gone, and she could distinguish between gross objects, and recognize colors. From now on and through the day she was plied with water by mouth and five injections of 400 cc. each of the above sodium carbonate-sodium chlorid mixture were given by rectum. These were well retained. Urine was voided about every three hours, and in increasing quantity. By midnight, that is to say in the first twenty-four hours after the intravenous injection, she had voided 572 cc. not counting two "large" voidings that were lost. The later portions of this urine were clearer in color and contained much less albumin than the specimens already described.

In the night of October 5, the patient went into labor, and at 8 A.M. forceps were introduced and she was delivered of a macerated fetus.

In spite of the exertions of labor she passed 320 cc. of urine between midnight and the time of the delivery of the placenta. Through the night the alkali-salt enemas could not be retained, but through the day she took and retained four enemas of 400 cc. each. In this second period of twenty-four hours she passed 734 cc. of urine. After delivery, her temperature, which on the night before had risen to 103.6° F. (by mouth), fell to normal.

In the twenty-four hours of October 6, she received and retained four enemas of 500 cc. each of the alkali-salt mixture, and drank freely of water (a glass every hour). She passed in this period 1840 cc. of urine, not counting two voidings that were lost with the stools. The later portions of this urine contained only a little albumin. The patient was sleeping well, and relishing her toast, gruel, eggs, milk, and broth.

In the next two days the alkali-salt enemas were reduced to two daily, one night and morning, and then stopped entirely. She was given a liberal diet, and water was insistently given by mouth. Lemonade and orangeade were urged. When the alkali was no longer given by rectum, sodium carbonate (0.5 gram) was given in a glass of water as often as the patient would take it both day and night, and she was asked to salt her food liberally. Her urinary output on this régime was as follows:

October 7	3616 cc.	October 14	2400+ cc.
October 8	3264 cc.	October 15	4096+ cc.
October 9	3520 cc.	October 16	3808 cc.
October 10	2528 cc.	October 17	3200 cc.
October 11	2108 cc.	October 18	1920 cc.
October 12	2396+ cc.	October 19	1915 cc.
October 13	2432+ cc.		

The great rise in urinary output on October 15 followed an increase in the amount of alkali and salt given by mouth; the fall on October 18 a reduction of this.

The œdema had disappeared and the albumin dwindled to a trace by October 7. This trace persisted up to October 19. The patient developed a slight temperature (100.8° F.) on the fourth day after delivery, but following intrauterine douches with bichlorid of mercury and iodin this fell so that only a temperature of 99° or 99.2° was registered in the afternoons up to October 17. From October 16 she was given an unrestricted diet, and on October 17 she sat up for the first time. On October 24 she "is downstairs, voiding an abundance of urine and happy." Recovery was complete.

Case XX.—(Dr. E. A. Majors, Oakland, California.). Mrs. A. B., pregnant for the second time and at term was found in labor and delivered, of a healthy living child, in an entirely normal way at 1 A.M. No previous history was obtainable. Following labor she fell into a deep sleep and at 5 A.M. it was impossible to arouse her. As there was no evidence of urinary secretion, she was catheterized at 6 A.M.

No urine was obtained. At 7 A.M. she had two severe convulsions. Following this she lay in a deep stupor with rapid breathing. At 10 she was again catheterized, but no urine was obtained. She now received by slow injection into the rectum the following:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	15 grams
Sodium chlorid	14 grams
Water, enough to make	1000 cc.

Sixty cc. of urine were obtained an hour after the beginning of the injection, and half an hour later another 130 cc. filled with albumin and casts. At the same time the patient began to clear mentally. Three hours after beginning the injection she would respond to questions. From this time on she was plied with water by mouth. Later in the afternoon 500 cc. of the above formula were again given by rectum and this was repeated next day. In the first twenty-four hours 1525 cc. of urine were obtained, and in the second 2240 cc. At the same time the albumin and casts diminished and on the third day the urine cleared entirely. Uneventful convalescence followed.

CASE XXI.—(Dr. C. C. FIHE, Cincinnati, Ohio.) Mrs. E. J. H., aged twenty-six years, showed much albumin and many casts in her urine, and developed a generalized œdema in the seventh month of this, her first pregnancy. Her urinary output was scanty and highly colored, and she felt herself below par. Her physical activities were much restricted, and she was placed on an active alkali therapy. Vegetables and sweet fruits were urged upon her, sodium phosphate and citrate were frequently given, and at regular intervals sodium carbonate and sodium chlorid were administered in capsules followed by water. Her symptoms cleared markedly, and she was carried to term, voiding 700 to 1500 cc. of urine daily.

At midnight, February 1, she went into labor, and at 8.30 A.M. was delivered of a living child. She had passed no urine the day previously, and none was passed during these hours. A gradually increasing blurred vision in her right eye, of which the patient had complained for several days past, had increased. She complained of headache. At 11 A.M. a convulsion lasting ten minutes occurred, and at 2.30 P.M. another lasting twenty minutes. At both times chloroform was administered. She was catheterized and 30 cc. of dark brown urine filled with albumin were obtained. At 5 P. M. catheterization was dry. The pulse ranged between 148 and 92. At this time 150 cc. of the following solution were given intravenously:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	10 grams
Sodium chlorid	14 grams
Water, enough to make	1000 cc.

A severe convulsion occurred while the intravenous injection was being made, and so this had to be discontinued. 0.015 gram morphin

was given hypodermically, and another 250 cc. of the solution were injected into the rectum. At 8.15 P.M. 1200 cc. of urine were obtained by catheter from the bladder. At 8.45, 1200 cc. of the above solution were given intravenously. An unmeasured amount of urine was passed with a stool at 10.30. At 11, 1022 cc.; at 12.30, 96 cc.; at 2.40, 16 cc.; at 6.40, 512 cc. were passed voluntarily. The pulse gradually fell during these hours to 76. Sodium phosphate, sodium carbonate, and sodium chlorid were given in small doses at regular intervals by mouth, and after the first signs of a freer urinary output, water and milk were urged at hourly intervals. In the first twenty-four hours after the intravenous use of the alkaline hypertonic salt solution, 4814 cc. of urine were passed, not counting two voidings that were lost. The patient's uneventful subsequent history is summarized below. Five grams each, per twenty-four hours, of sodium chlorid and sodium carbonate were given in divided doses in capsules followed by water, at regular intervals day and night. In addition, 15 grams of disodium phosphate were given once or twice daily, and for the patient's anemia, 0.5 cc. tincture of iron chlorid three times daily was prescribed.

Date.	Temperature.	Pulse.	Urine in 24 hours.	Albumin in grams per liter (Esbach).	Remarks.
Feb. 2–3	98.0° to 98.6°	78 to 80	4128+	1.0	Milk diet.
Feb. 3–4	98.2° to 98.6°	68 to 78	5578	0.5	Milk diet.
Feb. 4–5	98.2° to 98.6°	64 to 74	4127	0.5+	Light mixed diet.
Feb. 5–6	98.2° to 99.2°	72 to 86	5382	0.5	Light mixed diet.
Feb. 6–7	99.0° to 100.2°	74 to 86	4288	0.5−	Light mixed diet.
Feb. 7–8	98.6° to 99.6°	74 to 80	3904	0.25	Light mixed diet.
Feb. 8–9	98.0° to 98.6°	68 to 75	5272	Trace	Light mixed diet.
Feb. 9–10	98.6° to 99.0°	68 to 72	4032	Trace	Light mixed diet.
Feb. 10–11	99.8° to 98.0°	70 to 72	2200+	Trace?	Light mixed diet.
Thereafter until March 10	Normal	Normal	1700 to 2700	No albumin	No dietary restrictions.

Case XXII.—(Dr. W. A. Clark, Oakland, California.) The history of Mrs. H., aged twenty-three years, as well as it could be obtained, brought out the fact that she had been markedly œdematous and had had headaches and a scanty urinary output for several weeks past. At 5 P.M. of November 14, 1911, she gave birth to her first and living child. At 9 she had a convulsion that lasted fifteen minutes, and four more occurred in the night. She became unconscious. At 7 the next morning she was removed to the hospital. A severe convulsion occurred in the ambulance, and five more before 7.30 that evening. The patient vomited several times, the pulse ranged between 140 and 160, the respiration was 36 and the unconsciousness continued. In these twenty-seven and one-half hours she was effectively sweated several times, two magnesium sulphate and glycerin enemas were given, and two liters of 0.85 per cent sodium chlorid solution were given subcutaneously; 210 cc. of bloody urine filled with albumin were obtained by catheter during these hours.

At this time two liters of the following solution were given intravenously:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	10 grams
Sodium chlorid	14 grams
Water, enough to make	1000 cc.

An hour later on involuntary urination occurred, of which only 320 cc. were caught; at 10.30 occurred a second, and at 11.30 a third. At 2.15 in the night the patient was rational for a few minutes, and at 8.30 A.M. she awakened completely. Through the day she was given 1000 cc. of the above formula by slow drip into the rectum, and water by mouth *ad libitum*. The total urinary output in this twenty-four-hour period was 3986 cc., and except for the first specimens which were bloody, the urine was fairly clear, intensely acid, and filled with albumin and casts of all kinds. The pulse which at the time of the intravenous injection was 140, rose to 150 after the injection, to fall gradually to 102 by the next morning.

In the next twenty-four-hour period the injection by rectum of the alkaline hypertonic sodium chlorid solution was continued, about 300 cc. being injected and retained every six hours. Alkaline water by mouth was freely urged day and night. At 8 A.M. of November 17 the urine was neutral for the first time, and of a clear amber color. The total urinary output for this twenty-four-hour period was 3300 cc., with considerable albumin still present.

The history of the next five days is indicated in the following summary:

Date.	Temperature.	Pulse.	Respiration.	Urine in 24 hours.	Character.	Remarks.
Nov. 18	99.4°–97.8°	104–84	24–20	3840+	Dark amber to clear. Neutral, no albumin.	600 cc. alkaline hypertonic salt solution by rectum. Glass of alkaline water every half hour, day and night, by mouth.
Nov. 19	99.8°–97.8°	108–92	20	5216	Clear, neutral, no albumin.	Œdema of limbs subsiding. Solid food allowed. Alkali by mouth only.
Nov. 20	99.8°–97.4°	108–88	20	3552+	Clear, neutral, no albumin.	Œdema of limbs subsiding. Solid food allowed. Alkali by mouth only.
Nov. 21	99.8°–97.8°	112–88	20	3840	Clear, neutral, no albumin.	Œdema noticeable in flanks only. Gone from rest of body. Alkali by mouth only. On light general diet.
Nov. 22	98.4°–98.0°	100–80	20	3600	Clear, neutral, no albumin.	Œdema entirely gone.

From this time on until her discharge from the hospital, December 5, her history was uneventful. Her diet was unrestricted except that alkali was added to her drinking water, given both day and night, and she was urged to salt her food.

Case XXIII.—(Dr. N. A. Hamilton, Franklin, Ohio.) During the last week of her pregnancy, Mrs. M., aged twenty-nine years, had œdema of the legs, and suffered from impairment of vision to the extent of not being able to recognize her friends on the street. Her urine during this period was not brought to her physician for examination, though previous examinations had been negative. At term, on March 24, she went into labor, and was delivered normally of a living child by Dr. S. S. Stahl. The delivery occurred rapidly. The patient made normal progress until the fourth day (March 27), when she developed a temperature of 102° F., with a pulse of 110. This was attributed to an infection of the parturient canal. At the same time she became markedly nervous, complained of headache, and had great roaring in the ears. The urine became very scanty, and heavily charged with albumin and casts. This condition continued until March 31. On this day the pain in the head became very severe, nausea and vomiting occurred, and a marked numbness of the right arm and leg developed. The patient was pale and generally œdematous. There was a twitching of the muscles in various parts of the body. At noon on this day an active administration of sodium carbonate and sodium chlorid by mouth (0.33 gram each, every hour, with half glass of water) was started, and on the succeeding day this was given in the following form by rectum:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	10 grams
Sodium chlorid	14 grams
Distilled water, enough to make	1000 cc.

In the twenty-four hours during which the sodium chlorid and sodium carbonate were given by mouth, the patient's condition improved only slightly. On the following day, when administration by rectum was commenced, a rapid clearing began. The patient's history is summarized in the following table.

24-hour period ending	Highest pulse.	Highest temperature.	Urine.	Medication.	Remarks.
April 1	110	102.0°	720	Salt and alkali by mouth.	Signs and symptoms as above. General twitching. Much albumin.
April 2	115	102.2°	3420	Salt and alkali by rectum.	General symptoms better. Albumin less.
April 3	100	101.0°	2730	Salt and alkali by rectum.	Patient comfortable; no headache, nausea or vomiting. Œdema less. Albumin very much less in amount.
April 4	80	101.0°	3060	Rectal administration stopped. Alkali and salt by mouth only.	Same. Œdema lessening. Albumin in traces only.
April 5	78	101.3°	2700	Salt and alkali by mouth only.	Traces of albumin only.
April 6	84	101.1°	1680	Salt and alkali by mouth only.	No albumin or casts.
April 7	84	100.4°	1110	Salt and alkali by mouth only.	No albumin or casts.
April 8	80	100.4°	1530	Salt and alkali by mouth only.	No albumin or casts.
April 9	78	100.1°	1500	Salt and alkali by mouth only.	All œdema gone; patient feels entirely well. No albumin or casts.

The temperature continued a few days longer, but otherwise the patient went on to an uninterrupted recovery.

Case XXIV.—(Dr. Carl E. Curdts, Oakland, California.) Mrs. A. B. J., aged twenty-three years, entered the hospital, practically at term, in the early morning of July 14, 1912. She had always been well, and up to the eighth month of this, her first pregnancy had noted nothing abnormal. At this time her feet began to swell and her face became puffy, and some albumin and casts were found in her urine. In the ten days before entering the hospital she had been on a milk diet, and largely in bed. Nevertheless, she had grown progressively worse, her œdema becoming general and marked, and her urinary secretion dropping to "less than a pint measure" a day. Headache in the last two days had been constant. Her eyesight had been failing for a week past, so that on admission she could only distinguish light from darkness with her left eye, and with her right she could only recognize gross objects at a distance. In the last day before coming to the hospital, and during the morning at the hospital she complained of "twitching and nervousness."

At noon of her first day in the hospital she passed 90 cc. of urine—the first since the night before, according to her statement. This urine was deep amber, rather syrupy, and acid to paranitrophenol. On boiling with acetic acid the urine set into a solid jelly. An Esbach determination, using citric-picric acid as the reagent, showed 14 grams of albumin to the liter. The urine was filled with casts, mainly hyaline. The patient's pulse was 102, her temperature normal.

While immediate delivery by vaginal Cæsarean section had been recommended, it was felt, for reasons to be discussed later, that no such immediate haste was necessary. She was, in consequence, given the following formula by slow drip into the rectum:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	10 grams
Sodium chlorid	14 grams
Distilled water, enough to make	1000 cc.

She took the drip well, and in the course of the afternoon absorbed and retained 720 cc. At 3.30 p.m. she voided 378 cc. of urine; at 6.45, 300 cc.; at 8.55, 90 cc.; and at midnight 315 cc. The patient's pulse gradually fell to 82 by 5.30, and remained here. At the same time she volunteered that her headache was much improved, and that she could see more clearly. In the night of July 15 she was given 420 cc. more of the solution by rectum. At 2.30 a.m. she voided 150 cc. of urine; at 4, 60 cc.; at 8.30, 120 cc.; at 10.20, 60 cc., and at noon, 63 cc. The total urine for these first twenty-four hours in which the alkaline hypertonic sodium chlorid solution was given was, therefore, 1536 cc. In spite of the disturbance incident to giving her the solution, the patient insisted this morning that her headache was almost gone, that her eyesight had greatly improved, and that she felt more comfortable than for several days past. The urine had gradually decreased in acidity, so that the second specimen obtained after starting the drip

was neutral to litmus. The ESBACH determination showed a drop to 7.5 and 6.5 grams of albumin to the liter. The later specimens of urine clearly indicated that a higher salt concentration was prevailing in the body because the albumin on boiling with a drop of acetic acid no longer jellied, but was precipitated in flocculent masses.

In the early afternoon of July 15 the patient experienced some uterine pains, which gradually became more severe. Because of them the rectal injections were stopped. The patient was given as a substitute 8 grams of sodium citrate daily, by mouth in several small doses. At 7.30 P.M. the pains became very severe and frequent, and at 11.30 she delivered herself of a healthy, living, male child. Ether was administered, and forceps were used to accelerate labor after the head appeared at the vulva. In the hours while the pains were on, the patient's headache increased, but otherwise she continued to feel well. The pulse rose from 82, when the first labor pains were felt, to 102 between the pains, when delivery was in actual progress. Up to the time of delivery she passed 270 cc. of urine, and at 10.30 the next morning 340 cc. were obtained by catheter. Both these specimens were dark amber, intensely acid to methyl red, and barely alkaline to paranitrophenol, gave a heavy curdy precipitate on boiling with acetic acid, and showed 15 grams of albumin to the liter (ESBACH). Every field of a centrifuged specimen contained dozens of hyaline and finely granular casts. At this time her headache was slight, her eyesight more blurred than before labor, her temperature normal, and her pulse 88.

At noon of this day, July 16, she was again started on the alkaline hypertonic sodium chlorid solution, and in the course of the afternoon absorbed 570 cc. At 4.15 she was catheterized and 690 cc. of urine were found, and at 11 P.M. another 780 cc. were obtained. The first of these specimens was paler than previous specimens, was still decidedly acid to litmus and methyl red, and contained 5 grams of albumin to the liter. Many granular and hyaline casts and red and white blood corpuscles could be found in the sedimented urine. The second specimen was alkaline to methyl red and neutral to litmus and the ESBACH determination showed 2.25 grams of albumin to the liter. Only isolated casts could be found in the centrifuged specimen. The patient was now given 2 grams of sodium citrate by mouth every four hours, and milk and lime water every two hours. Through the night and up to noon of July 17 she passed 1770 cc., making a total for this twenty-four-hour period of 3240 cc. This night and morning urine was clear, neutral to litmus, alkaline to methyl red, showed a few granular and hyaline casts, and contained 1.75 grams albumin to the liter. The patient slept fairly well, said her headache was almost gone, and that she could again recognize the details of her surroundings. At noon she had no headache, could read the smaller letters of a newspaper, and showed a decided decrease in her general œdema.

She was now given an unrestricted diet, to which she was urged to add plenty of table salt. Vichy water was urged upon her, to which several grams of sodium citrate were added. To the milk which she

consumed lime water was added. Her history is summarized in the following table:

For 24-hour period ending at noon.	Total urine.	Grams albumin per liter (Esbach).	Remarks.
July 18	3280	2.0	Unrestricted diet, Vichy water, milk with lime water and 8 grams of sodium citrate per 24 hours. Some casts and white blood cells.
July 19	2520+	2.0	Unrestricted diet, Vichy water, milk with lime water and 8 grams of sodium citrate per 24 hours. No general œdema visible. Eyes slightly puffy. Good appetite. Feels well.
July 20	2366+	2.5	Unrestricted diet, Vichy water, milk with lime water and 8 grams of sodium citrate per 24 hours.
	contaminated with lochia.	One specimen only.	All signs of œdema gone. Only occasional cast in centrifuged specimen. Some red and white blood corpuscles. Urine neutral. The albumin does not precipitate easily on boiling.
July 21	3000+	1.7	No casts. Diet, Vichy water, etc., as before. Sodium citrate stopped and 0.7 gram of calcium chlorid every two hours day and night substituted for it. Urine faintly alkaline. Albumin comes down readily on boiling with acetic acid. Pulse 78; temperature normal.
July 22	2300+	1.0	No casts. Diet, Vichy water, etc., as yesterday.
July 23	2250+	Trace	No casts.
July 24	1980+	Trace	No casts. Calcium discontinued.
July 25	2400+	0	Urine negative.
July 26	2136+	0	Urine negative.
July 29	2346	0	Urine negative. Left hospital.

At the present writing this patient is entirely well.

§ 5

We move from the protracted case of nephritis which is the result of a lasting intoxication of some kind by imperceptible steps over into the chronic nephritides. But as soon as we discuss the chronic nephritides we find that we have to distinguish between those which represent a mere continuation of what was once a more acute process (the chronic parenchymatous nephritides, the secondarily contracted kidneys) and those which are chronic from the start, as in the type generally known as chronic interstitial nephritis (primarily contracted kidney) associated with changes in the vascular system. Very evidently, if our views are accepted, the nephritis which continues because of a protracted intoxication needs to be treated with alkali, salt and water in an equally protracted way. It has seemed to me that such a procedure yields good, and at times unexpect-

edly good, results, but I refrain from a detailed recital of such cases, for it is impossible, except as one works these things out for himself, to meet adequately the eternal argument that what has happened in such cases would have happened anyway.

There is at hand, as a matter of fact, no dearth of the most objective sort of clinical evidence indicating the great value of alkali administration in such nephritides. F. T. Frerichs [1] emphasized it in 1851 and the older generation of physicians bore him out in this.[2] A particularly careful clinical study of the effect of alkali on the signs and symptoms of nephritis was made more recently by Rudolf von Hoesslin.[3] He concludes that it is of great help in many cases, but fails in others, a view largely concurred in by such later studies as those of Glaesgen,[4] Ernst Romberg,[5] Fraenkel,[6] F. Conzen [7] and M. W. Scheltema.[8]

The use of alkali by many of these authors was purely empirical, and even the more recent studies do little to interpret the positive or negative findings beyond asking whether a relationship exists between the "degree of acidity" of the urine and the intensity of the albuminuria, the number of casts, the urinary output and the general symptoms of the patient. It would take us too far afield to give our own interpretation of the findings of each of the authors, but if in reviewing their contributions there is kept in mind what has been written in these pages apparent contradictions will quickly pass. As might be expected, the best results are always recorded when nephritides essentially toxic and evanescent in type are treated, while a persistence of casts, albumin, etc., is most definite when vascular and irremedial heart disease lie behind the urinary findings. In the former instance the "acidity" of the urine is an index

[1] F. T. Frerichs: Die Brightsche Nierenkrankheit, Braunschweig (1851).

[2] See, for example, the standard texts of Senator, von Leube, Rosenstein, Osler, and Dieulafoy.

[3] Rudolf von Hoesslin: Münch. med. Wochenschr., **56**, 1673 (1909); Deut. Arch. f. klin. Med., **105**, 147 (1912).

[4] Glaesgen: Münch. med. Wochenschr., **58**, 1125 (1911).

[5] Ernst Romberg: Deut. med. Wochenschr., **38**, 1073 (1912).

[6] Fraenkel: Deut. med. Wochenschr. **38** (1912).

[7] F. Conzen: Deut. Arch. f. klin. Med., **108**, 353 (1912).

[8] M. W. Scheltema: Toedienung van Alkalien bij Albuminurie, Delft (1914).

of what is happening in the whole kidney and a reduction in it is certain to be paralleled by improvement in urinary findings. When only pieces of the kidney are involved in consequence of blood vessel disease or localized infections, then the mixed urine coming from diseased and well kidney substance together may easily be neutral or even alkaline, and yet no impression be made upon the albumin output, etc. And since the so-called consequences of kidney disease are usually nothing of the sort they may, of course, appear with any kind of kidney findings.

Especially is it difficult to meet the argument that whatever improvement is noted in a nephritic would have occurred anyway when we deal with the chronic interstitial type associated with vascular disease. One can from the start foresee that such offers the least possible chance of being markedly benefited by an alkali-salt-water therapy, and in its final stages none at all. I have emphasized this repeatedly, and were it not for the fact that it is upon this very type of case that some of my critics have based their arguments, it would scarcely be necessary to refer again to some self-evident facts. How much and what can we do for such cases?

The primary change in chronic interstitial nephritis associated with vascular disease is not nephritis, but vascular disease. Every experimental fact and all physiological reasoning bears this out.[1] In consequence of the vascular disease one piece after another of the kidney suffers destruction. *And as this blood vessel disease cannot be and is not materially influenced by the injection of alkali, salt, and water, so also can this therapeutic procedure be of little or no use in this type of disease. The only cases in which it can be of service are those in which the blood vessel disease is in itself not wholly responsible for the observed changes, but where other temporarily active factors have been or are also responsible in bringing about our clinical picture.*

An illustration of this is offered in Case VIII, outlined above. Here to the picture of an established chronic interstitial nephritis associated with vascular disease, was added an intoxication with an anesthetic. The exacerbation is represented by the effects of the anesthetic upon the kidney, which effects are added to those already produced in this organ by the irremovable blood vessel disease. Cold, hard muscular work, an infection, or an

[1] See page 614.

alcoholic spree might have done what the ether did. And the alkali, salt, and water would have relieved the consequences of such added factors equally well; but blood vessel changes that permanently interfere with the blood supply to a portion or all of an organ, especially when we deal with end-arteries, are not relievable by any such schemes.

If this simple argument is borne in mind it will help to a better understanding of what may be, and what cannot be expected from the use of alkali, salt, and water in the chronic types of nephritis.

Incidentally, we can also see what may be accomplished for the œdema, whether involving an individual organ or the whole body, in any case of *heart disease*. The final picture of a chronic interstitial nephritis is half the time not that of a pure nephritis, but one of this plus a failing heart. Only too often is the last insult administered to a remaining nubbin of kidney that for years, maybe, has served to keep a patient alive, by the cardiac muscle giving way (with a resulting generalized lack of oxygen, abnormal acid production and accumulation in all the tissues of the body, and so an œdema). When a heart, from any cause whatsoever, drops below the lowest level of an efficiency necessary to maintain a proper circulation, and has no remnants of recuperative powers left in it, alkali and salt cannot supply them.[1]

[1] This is the type of case chosen by Joseph L. Miller (Amer. Jour. Med. Sci., **144**, 8 (1912), Jour. Amer. Med. Assoc., **58**, 1972 (1912)), upon which to test out the value of a salt-alkali therapy. According to his own statement, the majority of his cases were nephritides with permanently decompensated hearts. Naturally, alkali and salt could not produce a diuresis where the mechanism for water secretion was about gone. Only heart tonics such as caffein and its derivatives, drugs, in other words, which through their action on the heart and respiration assured a temporarily better oxygen supply to the kidney and body tissues generally, gave a temporary "diuresis." It was not necessary to be a believer in any of the colloid notions of water absorption to foresee all this, for, as we have known since 1860, an inadequate circulation will not allow even a normal kidney to secrete urine.

More recently L. H. Newburgh (Boston Medical and Surgical Journal, **169**, 40 (1913)), also concludes that the administration of alkali and salt is valueless or does actual harm in patients suffering from heart disease with broken compensation. To get at the real value of Newburgh's evidence one must center attention not on the apparently convincing argument presented in his main text, but upon the protocols attached thereto. While Newburgh claims to have kept his patients on a fixed dietary and medical

§ 6

Cases XXV and XXVI will illustrate the application of an alkali and salt therapy to clinical conditions which are, in general, regarded as consequences of an intercurrent "nephritis." To us they seem rather to illustrate the essential sameness that exists between that which in the kidney is called nephritis and that which in other organs goes by such special pathological or clinical names as cloudy swelling, stupor, coma, etc.; and as we found alkali and salts of service in the former, it will not surprise us to find them of service in the latter also.[1]

Case XXV.—(Drs. Charles G. Pieck and E. M. Baehr, Cincinnati, Ohio.) The patient, E. E., aged six years, had scarlet fever on May 19, 1912. The attack was characterized by an intense eruption, but relatively little fever, and no evident throat complications. He was up and around in less than a week. Twelve days later his mother called his physician because the boy had begun to complain of pain and distress in the throat. There was found an enlargement of the cervical glands, but nothing in the mouth or pharynx. The child grew worse during the week, becoming dull and listless, with no desire to eat, and sleepy and feverish. The boy's mother stated she knew he had not been passing a normal quantity of urine during this period.

This condition persisted for two weeks, the child growing more and more listless until he was in a continuous state of lethargy. He was asleep most of the time and had to be aroused to eat. Only upon becoming aware that his feet had become swollen did the mother call the physician a second time. At the time of his visit he found the child in a deep

régime and then tested out the value of alkali and salt administration by adding this or taking it away, he actually did not do so. His patients received daily, in addition to a standard diet, digitalis and half an ounce (15 grams) of magnesium sulphate. On his test days he drops the digitalis and magnesium sulphate and substitutes a few grams of sodium bicarbonate. Of course, the urinary output had to fall and the œdema to increase, for what Newburgh did was to substitute for the large dose of that most powerful protein dehydrant, magnesium sulphate, a small one of the weakly acting sodium salt, while removing entirely the cardiac stimulant which alone was whipping up the heart to a point where enough oxygen was getting into the kidney to allow it to secrete any free water that might be brought it. His clinical results, aside from being fraught with experimental errors which vitiate his conclusions, could all be foretold.

[1] In connection with the idea that coma is an œdema of the brain occasioned by an accumulation of acid in it, it is an interesting fact that one of the harshest opponents of such a conception, namely, F. Marchand, has himself reported (Münch. Med. Wochenschr., No. 4 (1912)) the case of a patient comatose from poisoning with sulphuric acid who roused almost immediately after sodium carbonate was injected intravenously.

stupor with marked swelling of the face and feet. Slight convulsive manifestations were apparent.

On the morning of June 25, almost one month, therefore, after the onset of the condition, the child was given an intravenous injection of two liters of the following solution:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	10 grams
Sodium chlorid	14 grams
Distilled water, enough to make	1000 cc.

No anesthetic was necessary, for the child was comatose. The veins were not collapsed and the injection was given more rapidly than usual, requiring but fifteen minutes. The child's mental condition cleared quickly, so that three hours after the injection he was able to recognize his surroundings and take water when asked to do so. In the twenty-four hours following the injection he was made to drink two liters of pure water. His improvement continued steadily. In three days the œdema had completely subsided, and the urine was flowing freely.

Samples of the urine obtained before the administration of the alkaline hypertonic salt solution were intensely acid and held albumin and casts in abundance. The urine obtained on the morning before the injection was begun showed casts as well as blood cells. Urine obtained a few hours after the treatment was alkaline and still contained albumin, but the casts had apparently disappeared. The mother stated that the child passed his urine on the morning following the injection after getting out of bed and securing the chamber himself.

The patient was kept in bed for four weeks, and the recovery was rapid and uninterrupted. The urine remained alkaline to methyl red during this entire period. Albumin persisted in every sample examined, but no casts could be found. The quantity of albumin was always less than 1 gram as measured by the Esbach method. At the present writing (October 22) the boy is entirely well generally, but still has a small amount of albumin in his urine.

Case XXVI.—(Drs. G. M. Allen and E. M. Baehr, Cincinnati, Ohio.) The patient, W. S., was a boy aged seven years, who had never before been ill. On December 10, 1911, his mother observed that he was ailing, tired, and listless. He complained of some distress in his neck below the left ear, where there could be felt an enlargement of the cervical glands. A low-grade fever was present at this time. His throat and ears were examined but nothing unusual was discovered. This state of affairs continued until December 27, when his temperature rose to 103° F., and albumin and casts appeared in abundance in the urine.

The following is a brief synopsis of the development and course of the case:

From December 27 to January 3, 1912: The temperature ran an irregular course varying in intensity from 99° to 104° F. The average quantity of urine passed in twenty-four hours was 416 cc. Albumin

and casts persisted. During this period he was given daily per rectum an average of 500 cc. of the following solution:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	10 grams
Sodium chlorid	14 grams
Distilled water, enough to make	1000 cc.

To January 10: The fever persisted, but was lower than during the previous week, fluctuating between 99° and 102° F. He passed an average of 640 cc. of urine daily. Albumin was constantly present, but was less in amount than before.

On January 10 there was a slight transitory delirium; there was also observed a thin watery discharge from the left ear. The administration of the alkaline hypertonic salt solution was continued as before.

To January 13: The temperature subsided gradually, reaching normal on January 12. The serous discharge from the ear continued. There was a leukocytosis of 34,000. On January 13, Dr. C. R. Holmes lanced the drums, but no pus was found.

To January 17: The temperature remained normal on January 12, 13, and 14, and the urine free of albumin. The patient voided about 400 cc. daily. At this time a slight œdema of the face was seen, most pronounced under the eyes. His mental condition was quite good; on the morning of January 16 his mother read to him from his books, while he commented upon the pictures. That night without warning he developed a generalized convulsion which lasted two hours. The left side, apparently, was the worse involved.

Dr. Holmes opened the left mastoid bone that night, the child having been given chloroform as an anesthetic. No pus was found. A second convulsion, lighter than the first, occurred later in the night.

On the morning of January 17 the temperature was 103° F. The child was in a stupor from which he could not be aroused except with difficulty. There were continued spasmodic twitchings of the left arm and hand, and it was noticed that he did not move these parts as he turned in bed. The left leg also was not moved as freely as the right. Urine was voided involuntarily. Albumin was present in considerable quantities.

At the request of Dr. Allen and Dr. Holt an intravenous injection was given by Dr. Baehr. One liter of the following solution was introduced into the superficial veins of the elbow.

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	10 grams
Sodium chlorid	14 grams
Distilled water, enough to make	1000 cc.

On account of the collapsed condition of the veins as well as the slight œdema of the tissues, the veins could be found only by dissection. No anesthetic was required.

During the ensuing night the patient was given 1600 cc. of water by mouth. In the course of the next twenty-four hours there were passed 1680 cc. of urine. Except in the earliest specimens there was no albumin

present even in traces. A blood examination made the morning after the injection showed a leukocytosis of 12,000.

To January 21: The child rallied a bit in the course of the next twenty-four hours, the pulse rate and vascular tone remained quite satisfactory, and the mental condition cleared a little. It could be discerned definitely at this time that there was a complete left-sided hemiplegia, the arm and the hand being more severely involved than the leg.

There was no fever, and the urine, for the most part, passed involuntarily, was of satisfactory quantity, and always free of albumin. On January 19 and 20 he became fretful and irritable, the œdema of the face became more intense, and a suspicion was aroused that his vision had become impaired. On January 21 his general condition was bad; the pulse, which had been of excellent quality during the entire illness, now became very weak and rapid, and he slowly sank into a stupor which was practically a coma. His pupils responded feebly if at all to light stimulation, and Dr. Holmes believed he was able to discern a congestion of the retinal vessels, although no extravasation or œdema of the discs was found.

After consultation a second intravenous injection of the alkaline solution was administered, this time in the right external jugular vein, as no other veins in the extremities could be located. Two liters were given. Chloroform was used as an anesthetic, chiefly to keep the child quiet during the operation. The coma seemed deep enough to allow of a much more severe manipulation. The entire time consumed was thirty minutes.

To January 30: In the first twenty-four hours he passed copious quantities of urine involuntarily. Water was given him to drink in large quantities, and milk alone was used for nourishment. Neither albumin nor casts were found at any time during this period. He was restless during the nights. His mental condition cleared rapidly. Three days after the injection a test of his vision was made. He was able to recognize his parents and the physicians about him.

Convalescence was slow though uninterrupted. Albumin never reappeared in the urine except upon one occasion when there was found a little circumscribed infection at the site of the first wound in the tissues of the elbow. As soon as proper drainage had been established the the albumin disappeared.

The child had lost greatly in weight and strength during these weeks, and the entire period of convalescence consisted in obtaining an improvement of these conditions. The paretic disturbance of the left arm and hand persisted, but showed a slight improvement from week to week.

During the following summer he was taken into the country about the Great Lakes, where he rapidly grew well. His father states that he left him there able to run about and paddle a canoe. The sole damage that remains is a tingling and stiffness in two fingers of the left hand.

§ 7

To this list in which the patients recovered I add a note on some acute nephritides in which the patients succumbed. A first fatal case is abstracted as Case XXVII.

Case XXVII.—(Dr. Elizabeth Campbell, Cincinnati, Ohio). Miss E. T., aged forty years, a school teacher, consulted her physician a month before entering the hospital because she was constantly tired. She was thin, but without other physical findings of an abnormal nature. The urine was entirely negative. She was given an iron tonic, and urged to take a rest and to increase the amount of her food intake. On this régime her general health improved. February 24, 1912, she entered the hospital complaining of a sore throat which had developed two days previously. Both tonsils were found enlarged and inflamed, and the lymphatic glands on both sides of her neck were swollen and tender. She suffered from pains in various parts of her body, and was nauseated. Her pulse was 112, and her temperature varied between 99.2° in the morning and 101.6° F. in the early evening. Her urine on the first half day after her entrance amounted to 300 cc., was dark amber, and acid, but free from albumin and casts. There was no œdema. She was kept at complete rest in bed on a milk and vegetable diet.

By February 28 her throat had practically cleared, the neck glands had decreased in size, and her general symptoms had improved. During this time she had taken frequent 0.3 gram doses of sodium bicarbonate with 0.25 gram doses of aspirin. Her temperature now varied between 99° in the morning and 100.6° F. in the evening. Her pulse ran between 96 and 112. On February 26 a trace of albumin was first noted in her highly acid urine as well as a few leukocytes. In the next two days the amount of albumin rose and granular, hyaline, and epithelial casts were noted. The urinary output per twenty-four hours was about 300 cc. At the same time diacetic acid and acetone in abnormal amount appeared in it. Sugar was absent as before. During these days the patient was frequently nauseated, and a marked generalized œdema developed.

From February 28 to March 7 the patient's temperature steadily declined, so that on this day it was normal. Her pulse continued high, 104 to 120. Beginning on February 28, 480 cc. of the following solution were administered daily by slow drip into the rectum:

Sodium carbonate ($Na_2CO_3 \cdot 10H_2O$)	10 grams
Sodium chlorid	14 grams
Distilled water, enough to make	1000 cc.

The urinary output in twenty-four-hour periods after this régime was instituted ran as follows: 330+ cc.; 480+ cc.; 540+ cc.; 725 cc.; 1080 cc.; 1140 cc.; 1050 cc.; 1035+ cc. The urine remained acid all the time that these injections were given, and acetone and diacetic acid continued to be present in abnormal quantities. The amount of albumin, which in the first three days of this period had been great, diminished

so that only a trace was noted in the later days. Medication during these days consisted of digitalin by hypodermic injection and occasional doses of strontium bromid at night.

On March 7, when I first saw the patient, her general condition was so good that I merely approved of the scheme of treatment that was being followed out. The rectal injections of alkaline hypertonic salt solution were continued as before. The day previously the patient had been drowsy, nauseated, and had had headache, but at the time of my visit the headache was less severe. That night she slept well. The following day she was uncomfortable because of an accumulation of gas in the bowels. Her temperature was normal and the pulse 108. The evening of this day and in the night she vomited, though the rest of the night she slept fairly well. During these two twenty-four-hour periods 1140 and 1275 cc. of acid urine were voided, containing only traces of albumin, very few granular casts, a few red and white blood corpuscles, and diacetic acid and acetone in excess.

The morning of March 9 was uneventful, but in the afternoon the patient began to complain of nausea. At 6 P.M. she vomited. The nausea and vomiting continued and became severe in the night. At 7 in the morning she complained of drowsiness; 1350 cc. of urine were voided in this twenty-four-hour period.

At 7.30 A.M. (March 10) the patient was unable to swallow some proffered milk, and at 8 A.M. the nurse noted that the patient "had a far-away look in her eyes, and did not answer questions." Shortly afterward the breathing became labored. At 9.15 the nurse noted that the now unconscious patient looked constantly to the right, and at 9.30 a convulsion occurred. The convulsions were very severe and lasting, and chloroform was administered to control them. Crepitant and subcrepitant râles could be heard throughout the chest. Two 10-drop doses of tincture of veratrum viride were given into the muscles of the thigh.

At 12, with no feeling that anything could be accomplished thereby, 1500 cc. of the alkaline hypertonic sodium chlorid solution were given intravenously. At 1.15, 300 cc. of urine were taken from the bladder by catheter, at 2.15 another 235 cc., and at 4.30 a final 75 cc. The first of these specimens, which included all the urine which had accumulated in the bladder since midnight, was heavily laden with albumin and casts. The second specimen contained relatively little albumin, the third again a large amount. All three specimens after the albumin had been removed reduced Fehling's solution heavily. The unconsciousness continued throughout the day, and the collection of fluid in her lungs increased. The patient could make no effort to cough it out, and the right to do a tracheotomy and practice insufflation was denied. Slight muscular twitchings were noted, but no more convulsive seizures. Oxygen played into the mouth helped but little. At 6 P.M., heavily cyanotic, the patient died.

Autopsy performed immediately after death showed a well-marked œdema of the superficial tissues. The peritoneal cavity was dry.

The kidneys were somewhat swollen and of good color. The capsules stripped easily. The liver was smooth and somewhat swollen, the cut surface dry. The spleen was swollen so that the capsule was tense, but otherwise showed no changes. The pleural cavities contained a few ounces of free fluid. The lungs, crepitated throughout, were heavy and ran fluid from their cut surfaces. The apices showed some flat, thick scars in the pleura. The pericardial cavity was empty, the pericardium smooth. The heart muscle was flabby and slightly grayish. The endocardium was normal. Permission to open the head was not granted.

In retrospect I feel responsible for the loss of this woman. In spite of the daily rectal injections of alkali, it is clear she did not get enough, as evidenced by the persistence of an acid reaction in her urine. I erred further on the day of my first visit in not completely ignoring her good urinary output, and directing all attention to the well-marked brain symptoms evident the day before. As I have previously said, the state of one organ as evidenced by its function is not an index in these cases of the state of another. The alkali and salt should have been more industriously pushed on the day of my first visit, and subsequently. The patient should, moreover, have been given an adequate amount of dextrose (glucose) by rectum or intravenously. Her small daily intake of food with persistence of diacetic acid and acetone in the urine clearly indicated that a starvation "acidosis" was being added to the other conditions conspiring to produce her fatal brain œdema.

§ 8.

There are certain types of acute nephritis in which the toxic agent is of a kind to lead to irreversible colloid changes in the kidney from the start and in which therefore a hope of relief is small from the outset. Bichlorid of mercury when absorbed in sufficient amounts belongs in this class, as does phosphorus. A number of my colleagues have nevertheless reported relief with ultimate recovery of the partial or complete suppression of urine in bichlorid poisoning. H. B. Weiss[1] has detailed astonishingly good results in some thirty odd hospital cases (with but two deaths) after employment of continuous sodium carbonate-sodium chlorid injections by vein or rectum, aided by the administration of potassium tartrate, sodium citrate and sugar by mouth. He

[1] H. B. Weiss: Jour. Am. Med. Assoc., **71**, 1045 (1918).

finds, quite naturally, that early treatment is better than late. The same beneficent effects of alkali administration were observed in experimentally poisoned animals by WILLIAM DEB. MACNIDER[1] who is frank in declaring this and other types of heavy metal poisoning (uranium) an acid intoxication. In one of my patients alkali, salt, dextrose, and water failed to elicit any response. She was seen for the first time in the third day of her anuria. When after twenty-four hours of alkali, salt and sugar intravenously no urine came, I urged a decapsulation, hoping to find a swelled kidney into which no blood was passing because of compression of the blood vessels. Instead, the kidney was soft, gray and mottled in spots and streaks with yellowish-white areas of "fatty degeneration."[2] The patient lived for nine days, in the course of which she developed no generalized œdema or any signs of a "uremia." Her blood pressure was normal at first, but fell on the eighth day. The volume of her pulse also fell slowly, disappearing at the wrist some eight hours before death. As the blood pressure fell her pulse rate increased and she became dyspneic. In this state, still clear mentally, she died.

Two cases of phosphorus poisoning in children who had sucked the heads off some phosphorus matches died in almost identical fashion, though the urinary suppression in these had never been absolute.

These three fatalities teach that not everything, including death, occurring in an individual showing casts and albumin, is at once to be regarded as consequent upon the kidney condition. The patients died of a "toxic shock" analogous to the "toxemic shock" that carries them away after the more protracted types of infection.

Early in the eclampsial series that I have seen, the following fatality occurred. The patient, practically at term, threw herself out of bed in a convulsion early one morning. She was brought to the hospital late at night after the convulsions and coma had lasted through the day. No urine had been obtained since the night before, and catheterization was dry.

[1] WILLIAM DEB. MACNIDER: Jour. Exp. Med., **23**, 171 (1916); Proc. Soc. Exp. Biol. and Med., **14**, 140 (1917); Jour. Exp. Med., **26**, 1 (1917); ibid., **26**, 19 (1917); ibid., **28**, 50 (1918); ibid., **28**, 517 (1918).

[2] For a discussion of what these changes mean physico-chemically see MARTIN H. FISCHER and MARIAN O. HOOKER: Fats and Fatty Degeneration, 9, 11, 76, New York (1917).

She was injected intravenously with 1600 cc. of an alkaline hypertonic salt solution at midnight. Her convulsions stopped, and she cleared mentally so that at 4 A.M. she talked to her nurse. Between midnight and 6 A.M. she passed 412 cc. of urine filled with albumin and casts. She had no labor pains. At this time she was given ether and a vaginal Cæsarean section was performed. There was marked hemorrhage, and at 9 she died.

It remains a question whether this should really be counted a failure. The fatality occurred eight years ago when I had less faith in the efficacy of a dehydration therapy and was less inclined than now to urge the quieter methods of delivery. The knowledge that an interruption of the pregnancy is synonymous with a cessation of the intoxication is a constant argument in favor of speed. In looking at this side of the picture we forget all too easily that *a third, and according to some statistics a half, of all the convulsive seizures occurring in pregnant women do not take place until after delivery*, in other words, not until the tremendous acid production of the muscular efforts of labor, the anesthetic, the bleeding, the pain, and the necessary surgical procedures has been heaped upon that already incident to the pregnancy itself. The injurious consequences of all these must be subtracted from what we gain by speed before we obtain a correct estimate of the value of our therapeutic procedures.

It is these facts that must also be kept in mind when the value of *capsule stripping* in nephritis comes up for debate. In at least some instances good has followed such a procedure. But this can be expected only if the deciding element between the recovery of the affected kidney and death is thought to be measurable in the increased circulation obtainable through the kidney by stripping the capsule. Even after the answer to this is given in the affirmative, then, before operating, the effects of the anesthetic and the shock of the operation must be considered, and not unless these are taken to be negligible should it be done, especially since experiment and clinical experience thus far are entirely one-sided in showing that all that can be gained through operation can be gotten by the simpler dehydration means of adequate alkali, sodium chlorid, magnesium sulphate and sugar administration.

These injections are also of service in surgical operations in which by accident or design the blood supply to the kidney

is temporarily occluded. The consequences of such a procedure are those of the experiments already detailed in which the blood vessels to the kidney were clamped. It has been shown by C. C. Guthrie[1] that perfusion with a physiological salt solution or a Ringer solution of kidneys so treated affects them more deleteriously than if they are left alone. This is not because the sodium chlorid is poisonous to the kidney, as Lawrence Litchfield[2] has maintained, but because these salt solutions are not sufficiently concentrated and alkaline to prevent the swelling, etc., of the kidney cells. Most perfusion mixtures moreover lack the necessary *colloids*—the water in them is free, which is not the case in blood and lymph.[3]

§ 9

A further recitation of cases could add little to what has been said. I should only like to emphasize once more the additional aid offered by a liberal use of the carbohydrates. When a desire for food is obtainable by an appeal to the appetite so that the gastro-intestinal tract can be used in normal fashion, cereals of various kinds, with sugar and salt work excellently. Candy in various forms is frequently desired and may well be given. Buttered and creamed toast, grapefruit juice with sugar, milk with milk-sugar added, etc., all not only prevent but help to relieve from a chemical point of view the "acidosis" so frequently observed in patients ill of any of a large number of causes.

When the normal route is inadequate or unavailable then the carbohydrate must be given by rectum or intravenously. But when this is done it must be given in an immediately utilizable form, in other words, as dextrose (glucose) of a high grade of purity. As *several hundred grams* are necessary to cover the daily demands of the resting adult individual, too much dextrose can hardly be given. In mild cases a continuous administration of dextrose with alkali is easily accomplished by rectum. *The alkali and sugar must never be mixed until immediately before*

[1] C. C. Guthrie: Arch. Int. Med., **5**, 232 (1910).

[2] Lawrence Litchfield: Jour. Am. Med. Assoc., **63**, 307 (1914).

[3] These truths are all being rediscovered in these days. What G. H. Whipple, H. P. Smith and A. E. Belt (Am. Jour. Physiol., **52**, 54, 72, 101 (1920)) describe as "plasmapharesis," namely, the effects following bleeding succeeded by the injection of Locke solution containing red blood corpuscles, is simply hemorrhage complicated by the effects of "free water" upon the body cells when deprived of an adequate circulation.

injection, as the alkali decomposes the sugar, and it is best, as a matter of fact, to alternate the two.

For intravenous use I give the dextrose alone. When alkali and salt are needed they are injected separately. In order to get as great a dehydrating effect as possible the sterilized dextrose solution is preferably given in highly concentrated form. Forty-five to ninety grams are dissolved in 100 to 200 cc. of freshly distilled water and injected *very slowly* (thirty minutes to an hour should be consumed) intravenously. To use haste is to lose the effect of the injection and to subject the patient to unnecessary risk.

8. Dehydration Therapy in Other Œdemas

Space does not permit a detailed discussion of the problem, but it must be apparent to the reader that this same alkali, salt and sugar therapy may be advantageously used (and empirically has been used) in a number of other clinical states in which a generalized or localized œdema is largely responsible for the signs and symptoms observed. It has already been shown how in the treatment of nephritis (œdema of the kidney) the same measures which bring about an improved kidney function, simultaneously relieve the "uremia" (œdema of the brain). The allegedly "uremic" symptoms are, however, only the clinical manifestations of a swelling central nervous system which will explain why a proper dehydration therapy will relieve such symptoms even when the mechanism producing such œdema is one different from that commonly associated with kidney disease. Administration of alkaline hypertonic salt solution works well in the brain œdemas following injury,[1] alcoholism,[2] arsenic (salvarsan) injections, etc.; in the delirium, twitchings and convulsions seen in the acute

[1] W. B. Cannon (Am. Jour. Physiol., (1901)) showed these to be due to changes in the brain itself. He held the increase in intracranial pressure to be due to an increased water absorption dependent upon an increase in the osmotic pressure of the cell contents. Brain swelling is more correctly interpreted as a colloid-chemical phenomenon. Cannon's work has scarcely received its merited recognition. Had it, we should have been spared much modern clinical and surgical teaching which still considers blood pressure the source of increased intracranial pressure. This is paramount to regarding the former as a source for energy greater than itself, for the swelling brain is able to shut off its own arterial blood supply.

A recent study of brain œdema in the terms of colloid-chemistry is that of J. S. Kopetzky (Trans. Am. Acad. Ophth. Oto-Laryn. (1913)).

[2] James J. Hogan: Jour. Am. Med. Assoc., 67, 1826 (1916).

infectious diseases; in the comas of arteriosclerosis, cerebral thrombosis and diabetes. JAU DON BALL[1] has used such therapy in various mental states having observed the periods of agitation and of depression in patients suffering from melancholia to be associated with an increase in blood pressure, their improvement with a fall. While originally inclined to attribute the changes in blood pressure to toxemic states influencing primarily the circulatory system, BALL[2] now believes that the increase in blood pressure is the response to an increased cerebral œdema. Decrease in this brain œdema then expresses itself not only through an improvement in mental symptoms, but in a fall of the blood pressure toward the normal. I have been informed that HARVEY CUSHING and E. C. CUTLER feed several teaspoonsful of table salt to their patients precedent to brain operations or afterwards, preventing in this way the tendency to cerebral hernia when the skull is opened. Their practice seems based on the similarly minded experimental studies of WEED and MCKIBBEN.[3] While these authors explain the effects of their injected hypertonic salt and baking soda solutions on an "osmotic" basis they are more logically corollary to the brain swelling experiments which MARIAN O. HOOKER and I detailed in 1912. Could more direct proof be found of the clinical applicability of the principles laid down in these pages?

The continuous administration of mildly hypertonic alkaline solutions (baking soda solutions) and the carbonates of calcium and magnesium has also proved of service in scurvy; in angioneurotic œdema; in the marasmus of infants and children; in bronchial asthma; it frequently relieves the labored breathing of arteriosclerosis[4] and heart disease. C. C. FIHE has obtained excellent results by using alkalies and salts in hay fever and mucous colitis, as has, in the latter condition, W. S. KUDER.

When one deals with readily accessible œdemas, one can observe directly the good effects of alkali and salt when applied locally.

[1] JAU DON BALL: Am. Jour. Insanity, 68, 661 (1912).

[2] JAU DON BALL: Personal communication (1918).

[3] LEWIS H. WEED and PAUL S. MCKIBBEN: Am. Jour. Physiol., 48, 531 (1919).

[4] Dyspnea in arteriosclerotics is most commonly due to the high acid content of the blood secondary to cardiac insufficieny. It may, however, be secondary to an œdema of the lung dependent upon *arterial disease of the bronchial arteries*, or an œdema (acid intoxication) of the medulla, itself dependent upon arterial change in the cerebral vessels.

A. E. Wright, J. L. Lohse[1] and James J. Hogan have long employed alkaline hypertonic salt solutions (as 1 per cent sodium citrate and 2 per cent sodium chlorid, or 2 per cent sodium citrate and 1 per cent sodium chlorid) in all manner of superficial injuries, burns and infections as a wet dressing.[2] A saturated solution of magnesium sulphate produces a similarly agreeable dehydration of the tissues. This explains its long recognized virtues in reducing swollen rheumatic joints, etc. One can by wet bandaging with either of these solutions easily reduce the œdema of a vulva, penis or scrotum as observed in heart or kidney disease or in conjunction with certain infections. John D. Long has injected sodium citrate and similar salts into the œdematous tissues in acute and chronic joint affections and attributes more than theoretical value to the observed reduction in swelling thus obtained. And have we not long recognized the agreeable effects of applying mild alkalies to flea bites, mosquito bites and urticarial wheals and the value of using alkalies and calcium chlorid internally? Is the reduction of these annoying œdemas any different from the reduction by like means of those produced experimentally on gelatin plates? At the same time such experiences yield ocular evidence of just what we are trying to do to internally situated organs when by any means we increase the alkali and salt content of the body tissues by administration of such by mouth, rectum, or intravenously.[3]

The large number of clinical conditions, involving so large a variety of organs, in which an alkali and salt therapy proves of service may seem at first sight somewhat strange. Surprise will disappear if we remember that the observed changes are merely a response to "injury." Whether such was induced by chemical,

[1] J. L. Lohse: Lancet-Clinic, **107**, 649 (1912).

[2] While I am not myself prepared to say that the antiseptic action of various dressing fluids is entirely without value, it is true that all the pure and derived hypochlorite (Carrell-Dakin) solutions of the war represent, as used, *hypertonic alkaline mixtures*. Those who have used sodium chlorid-sodium citrate solutions, for example, with the same surgical care as is employed when the hypochlorite mixtures are called into play pronounce the former not only less irritating and destructive to tissue, but as effective in the bacteriological cleaning up of infected wounds. W. H. and N. B. Taylor (Jour. Am. Med. Assoc., **74**, 1704 (1920)), while holding that antiseptics "are not contraindicated" recommend 10% NaCl for wound irrigation which "does not waterlog tissues" and has furnished "the most phenomenal results."

[3] See in this connection the interesting experiments of Chiari and Januschke (Wien. klin. Wochenschr., **23**, 12, (1910)), who observed the œdema of the conjunctiva following instillation of mustard oil to be markedly decreased or entirely suppressed through sufficient calcium administration.

thermal, mechanical, or other means, it is always associated with an abnormal production and accumulation of acid in the injured part, as clearly evidenced by the electrical change called the "current of injury." Most injuries to protoplasm are met by a reaction which in pathology is called "inflammation,"[1] the most constant sign of which is, as we would expect, a "swelling" of the injured part, in other words, an œdema.

9. On Œdema as an Alleged Consequence of Sodium Chlorid Retention

It has been noted by different authors that in œdemas of various types, as in those associated with certain types of nephritis, with heart disease, etc., there is evidence of chlorid retention in the body. From this it has been quite generally concluded that in these conditions the kidneys are unable to eliminate chlorid (or, as ordinarily stated, are unable to eliminate sodium chlorid) and that its retention in the body is responsible for the œdema. Upon such reasoning has been based the widely approved therapy of sodium chlorid restriction, and since a lessening of œdema has at times been observed in patients following such restriction, the argument as a whole has been regarded as entirely sound.

Against it have stood the failure of good observers to see any clinical improvement following careful efforts at applying the principles of sodium chlorid restriction, and the experimental facts developed in this volume, which have all gone to show that the presence of salt, including sodium chlorid, in simple proteins, or in living cells, tissues, or organs always reduces the amount of water absorbed, either under normal circumstances or in states of abnormally great hydration (œdema). These considerations have compelled the conclusion that *sodium chlorid restriction as a scheme of therapy is not only wrong in principle but harmful in practice.*

It is the purpose of these paragraphs to indicate why sodium chlorid retention and œdema go hand in hand. *Sodium chlorid retention is not due to an inability of the kidney to eliminate it, but to a change in the proteins (and other colloids) of the body as a whole. Sodium chlorid retention does not lead to œdema, but the changes which lead to œdema and to sodium chlorid retention*

[1] For a stimulating discussion of the colloid-chemical changes of inflammation, see Paul G. Woolley: Lancet-Clinic, **109**, 360 (1913).

are the same, consisting, in the main, of an abnormal production and accumulation of acid in the body.

Proof of this may be brought from both a clinical and an experimental side. So far as the clinical aspects are concerned it is sufficient to emphasize that sodium chlorid retention is a constant accompaniment of all pathological conditions in which there is evidence of an abnormal production and accumulation of acid in the body, as betrayed through a persistently high hydrogen ion or titration acidity of the urine, an increased hydrogen ion acidity of the blood, an increased hydrogen ion acidity of the saliva or other secretions from the body, a high relative or absolute ammonia excretion in the urine, a low carbonic acid content of the blood or alveolar air, etc.[1] Because such acid intoxication is common to many different clinical states it is readily apparent why sodium chlorid retention has long been observed in pneumonia, in many of the infectious diseases, in the pernicious vomiting and intoxication of pregnancy (eclampsia), in the cyclic vomiting of children, in diabetes, in carbohydrate starvation, in the severer types of the circulatory disturbances, in the severer anemias, in poisonings with arsenic, lead, phosphorus, chloroform, ether, and alcohol, and in the generalized parenchymatous nephritides when accompanied by a generalized œdema. *The water retention likely to be observed in all these states is not secondary to the sodium chlorid retention, but both are due to the existent acid intoxication. The presence of acid in abnormal amount in the body not only increases the hydration capacity of the (protein) body colloids, but it increases at the same time their capacity for holding chlorid.*

Experimental proof of this may be easily brought. When protein (carefully washed fibrin or gelatin) is thrown into a salt solution, it not only absorbs water from the salt solution, but salt as well. Upon adding acid, the amount of water absorbed is increased, but the absorption of salt is also increased. The presence of acid, in other words, leads not only to greater swelling, but also to sodium chlorid retention. Experiments were made by placing weighed amounts of fibrin or gelatin in definite volumes of neutral or acidified sodium chlorid or calcium chlorid solutions of definite strength kept in carefully stoppered flasks. After varying periods of time the solutions about the swollen

[1] See the succeeding pages 765, 778 and 790 (footnote).

protein were filtered off and the chlorid in them determined by titration with silver nitrate according to VOLHARD'S method. The following experiments will suffice to illustrate the values obtained:

EXPERIMENT 101.—A dry gelatin plate weighing 0.813 gm. is placed in each of the following solutions:

1. 75 cc. m/6 NaCl+25 cc. H_2O.
2. 75 cc. m/6 NaCl+25 cc. n/10 HNO_3.

Titration (of an aliquot portion) of the surrounding fluids 19 hours later shows the former to contain 0.00303 gm. Cl (=0.005 gm. NaCl) more than the latter. In other words, the gelatin in the acid solution has absorbed this amount of Cl (or NaCl) more than the gelatin in the neutral medium. Twenty-three hours later the difference is still more striking. At this time the surrounding liquid in the first mixture contains 0.00606 gm. Cl (=0.01 gm. NaCl) more than the second, or, conversely expressed, this much more Cl (or NaCl) has been absorbed by the gelatin in the acid medium than by that in the neutral one.

EXPERIMENT 102.—Three grams powdered fibrin are placed in each of four flasks containing, respectively, the following solutions:

1. 85 cc. m/8 NaCl+15 cc. H_2O.
2. 85 cc. m/8 NaCl+ 5 cc. n/10 HNO_3+10 cc. H_2O.
3. 85 cc. m/8 NaCl+10 cc. n/10 HNO_3+ 5 cc. H_2O.
4. 85 cc. m/8 NaCl+15 cc. n/10 HNO_3.

Nineteen hours later the excesses of Cl absorbed by the fibrin in the acid solutions over and above the Cl found absorbed in the neutral mixture were, respectively, 0.00303, 0.004545, and 0.010605 gm., or, recalculated in terms of NaCl, 0.005, 0.0075, and 0.0175 gm.

EXPERIMENT 103.—Three grams powdered fibrin are placed in each of five flasks containing, respectively, the following solutions:

1. 40 cc. m/6 NaCl+10 cc. H_2O.
2. 40 cc. m/6 NaCl+ $2\frac{1}{2}$ cc. n/10 lactic acid+$7\frac{1}{2}$ cc. H_2O.
3. 40 cc. m/6 NaCl+ 5 cc. n/10 lactic acid+5 cc. H_2O.
4. 40 cc. m/6 NaCl+ $7\frac{1}{2}$ cc. n/10 lactic acid+$2\frac{1}{2}$ cc. H_2O.
5. 40 cc. m/6 NaCl+10 cc. n/10 lactic acid.

Twenty hours later the excesses of Cl absorbed by the fibrin in the acid solutions over and above the Cl absorbed in the neutral mixture are, respectively, 0.0010605, 0.0037875, 0.006969, and 0.0113625 gm., or, expressed in equivalents of NaCl, 0.00175, 0.00625, 0.0115, and 0.01875 gm.

It has been customary in the modern writings on chlorid retention to assume that it is retained as sodium chlorid, and

it is for this reason that in the experiments thus far detailed we have recalculated the value of the chlorid retention in terms of sodium chlorid. Chlorid is, however, better retained by acidified protein than by neutral protein even when it is offered in other form. Experiment 104 demonstrates the increased chlorid absorption under the influence of an acid in the case of calcium chlorid.

EXPERIMENT 104.—Three grams powdered fibrin are placed in each of five flasks containing, respectively, the following solutions:

1. 40 cc. m/6 $CaCl_2$+10 cc. H_2O.
2. 40 cc. m/6 $CaCl_2$+ $2\frac{1}{2}$ cc. n/10 HNO_3+$7\frac{1}{2}$ cc. H_2O.
3. 40 cc. m/6 $CaCl_2$+ 5 cc. n/10 HNO_3+5 cc. H_2O.
4. 40 cc. m/6 $CaCl_2$+ $7\frac{1}{2}$ cc. n/10 HNO_3+$2\frac{1}{2}$ cc. H_2O.
5. 40 cc. m/6 $CaCl_2$+10 cc. n/10 HNO_3.

Twenty-four hours later the excesses of Cl absorbed by the fibrin in the acid solutions over and above the Cl absorbed in the neutral mixture are, respectively, 0.00303, 0.004545, 0.00606, and 0.010605 gm., or, expressed in equivalents of $CaCl_2$, 0.004735, 0.0071025, 0.00947, and 0.0165725 gm.

It would take us too far afield to discuss why chlorid is better retained by protein in the presence of acid than in its absence. It is sufficient to point out that the observed behavior may be nothing but an isolated illustration of the adsorption of a dissolved substance by a colloid,[1] which, as is so frequently the case, is decidedly better when an acid is present than when it is absent.

To this effect may perhaps, be added a chemical one, for there exists evidence that an acidified protein combines chemically with neutral salts in a way that the "neutral protein" does not.

The increased amount of chlorid retained by proteins under the influence of acid is of a magnitude to cover easily any amount ever found retained by patients. Rarely are more than some 10 to 15 gm. of (sodium) chlorid held in the body. Choosing, for illustration, Experiment 101 as a basis for calculation, we note that at the end of nineteen hours the acidified gelatin has absorbed an amount of sodium chlorid in excess of that absorbed by the neutral gelatin, amounting to 0.61 per cent of the original dry weight of the protein. At the end of another twenty-three hours the figure has risen to 1.22 per cent. If we choose the

[1] See pages 210 and 642.

very liberal figure that but one-fourth the normal body weight is dry substance (of which more than 95 per cent is colloid) this means that a man weighing 75 kilos, developing the ability to retain even 0.61 per cent more salt, is already able to retain 114 gm. of sodium chlorid, or if the higher figure is chosen, twice this amount.

These experiments have also a general biological interest in connection with the question of the "permeability" of cells to different substances. It is scarcely conceivable that anyone will maintain gelatin discs or fragments of powdered fibrin to be surrounded by "membranes" and yet observations of the type described in these paragraphs when made upon living cells or tissues are constantly cited as "proofs" of the existence of "membranes" about cells and of their alterable "permeability." Thus, it has been argued that "living" cells are surrounded by "osmotic" membranes "impermeable" to sodium chlorid and to other salts, which become "permeable" upon the addition of acid or of substances which indirectly lead to a production and accumulation of acid in the cells (chloroform, ether, potassium cyanid, etc.). Would anyone by similar reasoning maintain that gelatin plates and fibrin flakes lying in a "physiological" sodium chlorid solution are "osmotic" systems surrounded by "impermeable" membranes which become "permeable" to sodium chlorid when an acid is added?

Perhaps these experiments will illustrate anew the fruitful consequences of the application of colloid-chemical principles to medical and biological problems. As they have proved adequate in the explanation of the many phenomena characteristic of water absorption they will also explain without contradiction the absorption and secretion of dissolved substances,

10. On the Treatment of Anasarca and Ascites. Comment on the Sodium Chlorid Restriction Therapy

§ 1

A generalized œdema is so prominent a feature in many patients afflicted with nephritis that it becomes at times itself an object of treatment. From what has been said it is clear that this generalized œdema is not to be considered a consequence of the kidney state as is so widely done, but that the "nephritis" is rather to be regarded as in good measure an œdema of the kidney and so as

part of the general process which gives all the rest of the body an increased water content.

Since both theoretically and practically it is found that the swelling of the kidney may be reduced through salts, the recommendation that the nephritic try to keep the salt concentration in his kidneys high follows as a matter of course.

The thought naturally suggests itself that the same scheme of treatment may be extended to his general œdema. While such a course has for decades been approved of empirically, as evidenced by the use of saline purgatives, saline diuretics, etc., in the treatment of œdema, a marked reaction against the giving of salts in nephritis and in the œdemas accompanying it and other pathological disturbances has more recently set in. Of the scores of salts that might have been attacked in this way, sodium chlorid has been especially marked out, and to-day it is a widely accepted belief that the presence of this particular salt in the body is responsible for the retention of water and so the œdema of nephritis, of certain cases of heart disease, etc. Evidence in support of this view has been entirely clinical.

From our knowledge of their general physico-chemical activities it cannot be understood why sodium chlorid should, of all the common salts that are found in the living organism, act in this specific way. That, as a matter of fact it does not, seems to me proved conclusively by everyday experience and the experiments detailed in this volume. Does the butcher not complain because his meats shrink when he salts them? And neither in the normal nor in the œdematous animal does an increase in its salt content, sodium chlorid included, lead to an aggravation of the œdema. When rabbits are injected with progressively stronger solutions of sodium chlorid they lose progressively more water (shrink),[1] while frogs developing a generalized œdema in consequence of poisoning with uranium (uranium nephritis (!) with casts, albumin and diminished water secretion), absorb decidedly less water if treated with sodium chlorid and other salts than when not so handled.[2] These remarks hold for all the tissues of the body. Evarts Graham[3] showed me recently a pair of guinea pigs which had been subjected to

[1] See page 331.

[2] See page 260.

[3] Evarts Graham: Personal communication (1914); Jour. Exp. Med., **22**, 59 (1915).

the same degree of chloroform poisoning. One was subsequently treated with alkali and hypertonic sodium chlorid, the other not. On autopsy the kidneys and liver of the untreated one were swollen, dry and strongly mottled with grayish white patches of necrosis; those of the treated were of normal consistence, bled normally and showed less evident patches of destroyed tissue.

The salts decrease œdema wherever found, including that of certain types of nephritis, and sodium chlorid is no exception to this rule.

§ 2

How best to deal with the accumulations of fluid which so often occur in the peritoneal, pleural and pericardial cavities in the œdemas associated with heart lesions, kidney lesions, etc., is a matter to which colloid chemistry can also give answer. We know, of course, that a considerable ascites, hydrothorax, or hydropericardium may develop and disappear without ever assuming enough importance to demand clinical consideration. At other times, however, they become so great that they of themselves give rise to trouble or at least add additional burden, as through their pressure effects, to the circulation, respiration, etc. *These so-called transudates are identical with lymph and blood plasma, and it is for this reason that they may persist for days, weeks, or months in the body cavities being without absorbed. They are colloid solutions in which the solvent is bound to the colloid, and not until the solvent is rendered "free" can it be absorbed. When nature does not spontaneously remove them they can be gotten rid of only by tapping.*

That this is true is borne out not only by our previously described experiments [1] but by the well-known fact that blood and lymph extravasations into the peritoneal, pleural or pericardial cavities, whether encountered in man or produced in entirely healthy animals, remain here unchanged and undiminished in amount for periods of time in which other aqueous solutions not containing such colloid material (which, in other words, contain "free" water) are readily absorbed. The following experiments prove this:

[1] See page 305 and the first edition of my "Œdema." See also James J. Hogan and Martin H. Fischer: Kolloidchem. Beihefte, **3**, 385 (1912).

Experiment 105.—A black and white rabbit is taken from its hutch, catheterized, and then weighed. Its weight is found to be 1493 grams. A slight opening is made in the abdominal wall and traction made on this so as to make the entrance of fluid into the peritoneal cavity easy. A second rabbit has the carotid laid bare for as great a distance as possible in the neck. It is ligated high up, an artery forceps is attached to the coat of the vessel, a small forceps is placed below this, and the carotid is severed. This second animal is now placed in such a position that the blood will flow directly from its carotid into the abdominal cavity of the first animal, when the forceps is removed. The blood passes in a stream directly from the cut artery of the second animal into the peritoneal cavity of the first. This procedure is carried out at 2.40 p.m. The abdominal wound is closed immediately and the animal is weighed a second time to see how much blood has flowed in. The second weighing registers 1504 grams, which means that 11 grams of blood have flowed in. At the end of an hour the animal is killed by a blow on the head and immediately autopsied. The blood is found uncoagulated in the folds of the intestine. It is carefully aspirated into a tared flask and weighed. 11 grams of blood are recovered.

Experiment 106.—In an entirely similar way a guinea pig, weighing 520 grams, has a small opening made in its abdomen, and the blood from the carotid of a rabbit is made to flow directly into it. An increase in the weight of the guinea pig of 2.3 grams is thereby brought about. At the end of $1\frac{1}{4}$ hours the pig is killed by a blow on the head and the unabsorbed blood is aspirated into a tared flask. 2.1 grams are recovered.

Experiment 107.—A black and white rabbit, weighing 1630.5 grams, receives intraperioneally in the already described way enough blood from the carotid of a second rabbit to raise the weight of the former 26 grams. At the end of an hour the rabbit is killed, and the unabsorbed blood is carefully recovered by aspiration into a tared flask. 26 grams of blood are recovered.

Experiment 108.—A white rabbit, weighing 767 grams, receives intraperitoneally 45 grams of blood from the carotid of a Belgian hare. At the end of seventy minutes the animal is killed by a blow on the head and the blood found in the peritoneal cavity is aspirated into a tared flask. 42.2 grams are recovered.

There is nothing strange in the fact that the removal at times of a comparatively small amount, say of an ascitic accumulation, may be followed by a rapid absorption of the rest. As the amount of fluid in a serous cavity increases, the circulation through the surrounding tissues becomes more and more embarrassed, and so the possibilities for absorption progressively poorer. To relieve this pressure even somewhat improves the

circulation, not alone as to quantity, but as to quality of blood passing through the part (a blood more nearly arterial in character replacing a highly venous one). By thus favoring the removal of carbonic and other acids always found in such serous accumulations [1] the power of the colloids here for holding water is decreased, and so further opportunity for the abstraction of water from the transudates found in these cavities is brought about. What holds for the "transudates" and their absorption holds also, of course, for the absorption of inflammatory "exudates."

Various authors have claimed that the administration of sodium chlorid (and other salts) is bad practice because it increases the accumulations of fluid in the serous cavities in the œdemas encountered in "parenchymatous nephritis," in heart disease, etc. How the salts may be effective in this regard is explained by the following. When any salt is given an œdematous individual his tissues give up water as do the frogs that have been described. But where does the water go? The body weight as a whole can diminish only if this water is lost from the body through the urine (skin, gastro-intestinal tract, or lungs). But in a generalized nephritis and in heart lesions the kidney does not so readily rid the body of water as in health, and so this freed water must go somewhere else. If it does not come out through some other emunctory (as in watery stools or sweat) *this water can only escape into the cavities.* What happens is identical with what is observed in experimental animals when they are made to give up their water very rapidly (especially after first rendering them œdematous by any means we choose) by injection of concentrated salt solution.

I saw a good clinical illustration of the process in a patient of W. S. Kuder. A woman who for several weeks had been in bed, suffering from an extensive generalized œdema, with collections of fluid in the pleural cavities and abdomen, secondary to a heart muscle insufficiency of several years' duration, had the abdominal effusion removed by paracentesis. In order to keep up the drainage some strands of silk were left in the opening made by the trocar. Seepage stopped at the end of twenty-

[1] G. Strassburg: Pflüger's Arch. **6**, 65 (1872); A. Ewald: Arch. f. (Anat. u.) Physiol., 663 (1873); Felix Hoppe-Seyler: Physiologische Chemie., **1**, 601, Berlin (1877).

four hours, but the silk was left in place. On the third day a liter of water containing 14 grams of sodium chlorid and 10 grams of crystallized sodium carbonate ($Na_2CO_3 \cdot 10H_2O$) was given intravenously to combat the tissue œdema. This went down enormously, and as it disappeared the abdominal wound began to seep once more so that pad after pad had to be applied to absorb the liquid. James J. Hogan observed the same in a ten-year old child with a practically complete suppression of urine following an infection of the kidneys, in which a drain was left in the abdomen following paracentesis for an ascites.

It is clear, therefore, that while the œdema of the tissues is reduced when salts (or alkali) are given an œdematous individual, the collection of fluid in the cavities may be increased. The thirst consequent upon the dehydration may lead the patient to drink water. In this way his total body weight (which in turn is taken as a measure of his œdema) may at times actually increase.

But such a secretion of fluid into the peritoneal or other cavity is not by itself a particularly serious thing, for water and various salt solutions are readily absorbed from the peritoneal (and other serous) cavities. If the effects are lasting it can only be because the added fluid has given rise to more permanent changes through added pressure, etc., or because it has had colloid material added to it (albumin) which after secretion renders the water unabsorbable. It is of interest to recall, after what was said regarding the origin of albumin in the urine, that the ascitic fluid may be looked upon as an albumin-containing secretion from the peritoneal tissues which, in its general composition and mode of origin, finds an analog in the highly albuminous urine secreted by the kidney in acute nephritis. Syneresis and a "solution" of previously solid colloids occur in both.[1]

How now, if these views are correct are we to explain the good results reported by Widal and his school when patients with œdema are salt restricted. *When the salt is taken out of the diet of a patient his appetite for water is tremendously decreased. If the patient is put upon the* Karell *dietary régime, care is taken from the start to assure not only a low salt intake, but a low water intake also. It is this water restriction in both cases that produces the reduction in œdema.*

[1] See pages 283 and 508.

We ordinarily overlook the fact that even under normal circumstances more than half the total water excretion is lost through the lungs and skin. Against the normal of, say, 1500 cc. of water lost as urine, man loses 500 cc. from his lungs, and 1000 to 2000 cc. through his skin. If the patient is in a warm room, or if he is warmly covered, or if, as is so frequently done, he is sweated, then these figures rise still higher. Even a completely anuric individual therefore suffers a substantial loss in weight if for any reason his water intake is restricted. But no colloid mass, be this a drying gelatin plate or a water-starved human being, loses its salt to the atmosphere as rapidly as it loses its water. The salts therefore become more concentrated in the cells and tissues of the body.

To realize what must be the effect of all this upon the total body weight is not difficult. Successive daily weighings will show such a patient to be losing a kilo or more a day, and this is exactly what these clinical observers report. What a good effect this or any other effective dehydration scheme must have upon a nephritic kidney, a swelled brain or any similar condition, can easily be appreciated when the vicious circles that may and do become established in any of these organs or in an extremity are kept in mind. I have repeatedly emphasized how an œdematous organ, not given free play to swell, tends to make itself progressively worse. As the organ swells, a hampering capsule, bony walls, or a small foramen make the swelling tissues compress the blood vessels entering the affected organ, and so a lack of oxygen, in itself capable of producing an œdema, is added to the already existing factors responsible for such. Thus, sweating, drink restriction, or salt restriction (which indirectly amounts to *drink* restriction) all lead to a drying out of the tissues. If now a kidney in its process of swelling, say from an intoxication of some sort, has succeeded in rendering itself anuric by squeezing upon its blood supply, a more normal state may once more be attained if we rob the body tissues and fluids of their water content, and so also draw upon the water content of the swollen kidney. The net result must be a better blood supply through the kidney, and if the initial insult to the kidney was not too severe or of too lasting a character, the restitution of a better circulation may well be equivalent to a relief of the kidney condition—just as when alkali and salt are gotten into this organ.

Then why not the salt restriction scheme of therapy? I would answer that salt restriction constitutes an unnecessarily roundabout and by no means pleasant way of accomplishing a water restriction which can better be obtained by direct means. Second, as previously emphasized, intoxication depends upon concentration. We can dull the effects of an intoxicant only by diluting it, and since we can guard ourselves against the bad effects of water by giving with it properly chosen salts in the right concentration, I have not been able to see the superiority of waiting for nature to dehydrate an organ which we can dehydrate as well and more rapidly, especially when in the former case we rob our patient of the advantage of having water available with which to float off his poisonous products.

I should like to re-emphasize a last point in this entire matter of alkali, salt, and water therapy. It must be remembered that no solution is either absorbed or secreted as such, but that in every case the water and dissolved substances move independently of each other, at times in the same direction, at others in opposite directions, and usually at entirely different rates. A primary purpose in giving the hypertonic solutions that I have advised is to secure an increase in the *salt* concentration in the body. Now the body cells and fluids in any state associated with an œdema have an increased capacity for holding water, and so take up water more easily than do the normal. *The œdematous individual will therefore absorb water from any given salt solution more easily than will the normal individual.* A solution, "hypertonic" for a normal individual, may be "isotonic" for one whose colloids have an increased hydration capacity. So it need not surprise us to find that when even a strongly hypertonic salt solution is given certain nephritics they may show an initial increase in their œdema. This only means that the colloids of their tissues were not previously saturated with water. Neither does it prove that the salt injected was responsible for this œdema, but only that *the concentration of the salt which we succeeded in attaining in the body was not sufficiently high to decrease the existent high hydration capacity of the colloids of those tissues which showed the increased swelling. To remedy the situation we must give still more salt.* (And at this time, as at all other times when we are trying to increase the absolute salt concentration in the body, we must give with the salt as little water as possible.)

XII

DIAGNOSIS AND PROGNOSIS IN NEPHRITIS

1. Judging the Nephritic. Prognosis

While the preceding pages will have made clear the meaning of the various signs and symptoms associated with the nephritic state and their significance for prognosis I am going to repeat here in rather dogmatic terms various facts because of their clinical importance and because I am constantly questioned regarding them.

§ 1

What, first, may be learned from *urinalysis*[1] in nephritis? The great truth to remember is that *urinalysis enables us to follow the course of pathological changes which may be occurring in a kidney and nothing else.* The most serious mistakes both in prognosis and treatment which the physician can make are dependent upon his attempts to judge from urinary findings alone whether his patient is going to develop "uremia," increased blood pressure, etc.—all of them things in no way consequent upon the kidney disease. The possibilities for such complications *must be discovered by other clinical methods.*

With this fact firmly in mind, it is of primary interest to discover whether the kidneys are functionally competent or not.[2] Any kidney which in putting out a satisfactory amount of water and in which such secretion may be maintained is functionally competent. *Use the ability of a kidney to put out water as the index to the amount of kidney substance not involved in a pathological process; the number of casts and quantity of albumin as an index to the amount that is involved.*

Practically expressed, the 24-hour urinary output should be determined. If the amount runs above 1000 cc. (34 ounces) it may be assumed that sufficient kidney function is left to be considered adequate. Any amount of urine above this daily liter is to be considered in the patient's favor so far as his kidney function is concerned. This is true even of the "chronic interstitial"

[1] Space does not permit a discussion of the urinalytic methods most important for the general man in medicine or surgery and their significance. I have done this elsewhere (see MARTIN H. FISCHER: Practical Urinalytic Methods, TICE's Practice of Medicine, **1**, 423, New York (1920)).

[2] See page 757.

nephritic whose kidneys are rarely (and then only terminally) physiologically inadequate.

If the water output falls below a liter daily it does not yet mean defective kidney function—it may simply be the result of excessive sweating, great catharsis or low fluid intake. The patient should therefore be given a half liter (16 ounces) of water to drink.[1] If the urinary secretion is definitely increased (by 400 to 500 cc. or 13 to 14 ounces) in the succeeding two hours (or certainly upon a second testing in similar fashion during a subsequent two hour period) the prognosis is favorable. If no such increased diuresis results the entire gamut must be run of causes lying (1) without or (2) within the kidney which may be responsible for such lack of function.

§ 2

What now does the discovery of casts and of albumin (of kidney origin) in the urine tell us? It merely tells us that destruction is occurring in the kidney and nothing more. It tells us nothing of the nature of the destroying forces nor of their importance from the standpoint of the patient. This information has to be worked out by other methods than urinalysis. Speaking generally, large numbers of casts and much albumin mean greater destruction than a smaller number with little albumin. Yet so far as the patient is concerned either finding may be of trivial or of great importance. The occasional cast with a trace of albumin may be of great importance if it is the expression of blood vessel disease, but not because of the kidney findings but because of the accompanying diagnosis of blood vessel disease. On the other hand, large numbers of casts with albumin in an active athlete or in a man who works to the point of becoming dyspneic (as in running for cars, making close connections, hard walking, etc.) may mean nothing, for any healthy man may get into such a state and over it in a few hours. Similarly, a man whom we first see in a convulsion and in whose urine we then discover casts and albumin must not at once be called a " chronic interstitial nephritic " the subject of a "uremic" attack. He may be such, but a convulsion from any cause (which really only means hard muscular work with respiratory interference) as an epileptic fit, the spasms of strychnin

[1] See page 760.

poisoning, or those consequent upon an infection, will put casts and albumin into a urine that never contained them before.

Only if no such temporarily acting factors are at work are an increase in casts and albumin to be regarded as significant. The nephritic who with bed rest and proper treatment shows increasingly larger quantities of casts and albumin, is certainly not getting better, but good judgment must be used before it is stated too flatly why the patient is getting worse. Especially is restraint in order before any change in the patient's general condition is said to be due to the more evident signs of kidney involvement. More casts and more albumin in the urine mean, of course, more kidney involvement, but only clinical judgment can say whether the added factors lie within the kidney itself or outside of it. A progressing blood-vessel disease may involve larger and larger areas in the kidney up to the whole organ; or an infection originally limited to a spot or a few spots may spread to involve the whole kidney. But all too often, especially in the so-common chronic interstitial nephritides associated with blood vessel disease, the increase in the casts and albumin coincides with the time the patient gets out of the ambulatory class, and the causes for the increase lie entirely outside of the kidneys. A failing circulation is discovered—a failing heart muscle with dilatation, leaking aortic and other valves, dilatation of the aorta itself, etc.—and the prognosis for the patient becomes that of his circulatory disturbances with little emphasis upon the kidney findings which *in toto* are now so largely dominated by and secondary to the heart failure.

It is a safe rule whenever confronted by a patient showing simultaneously the signs of heart disease and of kidney involvement to look upon the heart as the greater offender and not the other way around, as is so often done. The matter is of much importance from the standpoint of clinical diagnosis, prognosis and treatment. The problem is often brilliantly illustrated by some of the so-called "orthostatic" cases of albuminuria. Many of these are really undiagnosed cases of cardiac insufficiency. Such patients may not show a single abnormal urinary feature when at bed rest, but the increased work incident to mere maintenance of the upright position for an hour or two make albumin and casts appear and continue as long as the upright position is persisted in. In the ambulatory

nephritic presenting cardiac signs or symptoms or, to turn it about, in the cardiac patient showing albumin and casts in the urine I make use of the simple expedient of two or three days' rest in bed by way of estimating and eliminating the cardiac element in the production of his urinary signs. Many a patient with valvular disease, whose heart is efficient for certain low degrees of physical endeavor and in whom the cardiac process is not of a progressive type may be taught how to live and be given a more cheerful outlook upon life by not having a diagnosis of "BRIGHT'S disease" superadded.

But the impression must not be gotten from these remarks that a cardiac element is the only one which accounts for the orthostatic types of albuminuria, nor yet that all which is eliminated by bed rest is of cardiac origin. The blood of an anemic individual may supply his kidneys when at rest in bed with enough oxygen to keep the urine free from albumin, but prove inadequate when he assumes the erect posture with its increased need for oxygen; or kidneys which in the prone position are freely supplied with blood may yield albumin and casts because their blood vessels are dragged upon when the patient rises.

§ 3

The urinary findings are of much service in determining whether a generalized or a spotty type of nephritis is at hand. An involvement of the whole kidney brings with it a decrease in urinary output with many casts and much albumin; a normal water output with less albumin and casts obviously means that some of the kidney substance has escaped injury (for less than one-fourth the total kidney substance is sufficient to maintain the normal water secretion, and the albumin and casts are proportionate to the amount of substance that is being destroyed). A low water output should therefore lead to the diagnosis of *generalized kidney disease* (generalized parenchymatous nephritis); a normal (or increased) water output to a diagnosis of a *spotty affection* (infectious nephritis, chronic interstitial nephritis) with the amount of spotty involvement judged from the number of casts and amount of albumin. In the first instance search must be made for factors which are capable of thus affecting a whole kidney; in the second for such as can give rise to spotty types of disease.

Practically, the first calls for a recognition of all the causes capable of producing a generalized poisoning of the whole kidney, in the list of which may therefore be found the old "predisposing" guard of cold, hard work and a high protein diet; the more direct factors of heart disease, respiratory disease, hemorrhage or anemia; the direct kidney poisons beginning with the volatile and fixed anesthetics, passing through the heavy metals and ending with the soluble protein products produced through infection or through pregnancy (intoxication with foreign protein derived from the sperm?).

The diagnosis of such a generalized kidney disease is greatly aided by the discovery of œdema elsewhere in the body and the *absence* of any increase in blood pressure. (If there is an increase in blood pressure it must be determined whether this is due to an œdema of the brain or to vascular disease.)

The spotty type of nephritis has behind it either (*a*) an infection of the kidney or (*b*) vascular disease. The former again carries with it *no* increase in blood pressure. *The most significant diagnostic point indicative of this type of kidney disease is the presence of leucocytes in the urine.* The ordinary toxic types of nephritis (following heart lesions, mercury or arsenic poisoning, etc.) and the so-called chronic interstitial types associated with high blood pressure do *not* show appreciable numbers of white cells in the urine. To recognize the kidney associated with vascular disease the whole patient must be seen. The increased blood pressure, obvious vascular changes and cardiac hypertrophy being the real elements upon which a correct diagnosis is made. What is most important in this type of kidney disease is to remember that practically none of the things of which the patient complains or is the victim have anything whatsoever to do with the kidney disease. *The urinary findings tell what is happening in the kidney and nothing else.* If these are satisfactory the kidneys may be passed. If the patient is ill or dies, he is not dying of kidney disease. A normal or "increased" water output never means anything but good kidney function and the occasional cast and trace of albumin mean that very little kidney is undergoing destruction. There are no "masked" nephritides or "uremias without urinary findings." There are only deaths in patients in whom vascular disease may have affected the brain or heart or some other vital organ while leaving the kidneys untouched.

§ 4

As previously noted, the œdema observed in a sufferer from nephritis is never to be regarded as secondary to the kidney disease. In generalized parenchymatous nephritis the general œdema is simply due to the same cause as the œdema of the kidney. In the earlier stages of the chronic interstitial types of nephritis associated with vascular disease we are not in the habit of expecting an œdema. When these patients do show such it means exactly what a generalized œdema always means—a generalized intoxication of some type. Such may be any of the many kinds which overwhelm the previously normal individual, but in actual practice their origin, in the chronic interstitial types with blood vessel disease, is almost always traceable to something which can interfere with the normal (oxidation) chemistry of the whole body. The commonest of these are disturbances affecting the general circulation or respiration, wherefore careful consideration of the heart and its efficiency is not only demanded, but usually reveals the real source of the trouble. As a consequence of the cardiac disturbance with its resulting generalized œdema is to be expected an œdema of the kidneys whence the increased casts and albumin and the decreased urinary output. The patients with chronic interstitial nephritis associated with vascular disease rarely die of their kidneys. Exclusive of the fatal accidents which may overtake anyone and which are especially prone to attack the vascular case, as hemorrhage, thrombosis, coronary disease, etc., they die almost half and half of failing hearts which will not supply enough blood to keep the remains of their kidneys working, or of œdemas of the brain secondary to the vascular disease (and wrongly called "uremias"). *The prognosis of chronic interstitial nephritis associated with vascular disease is almost entirely the prognosis of vascular disease and of heart efficiency.*

§ 5

Exactly as our judgment of the chronic interstitial nephritic cannot rest too exclusively upon certain kidney findings, so also will their too intense contemplation in the parenchymatous types lead us into false paths. While in rare instances the kidneys may be picked out alone to exhibit the picture of a gen-

eralized parenchymatous nephritis, an intoxication is commonly at the root of the process, which affects simultaneously *all* the organs of the body. Hence the so common association of the œdema of the kidney with an œdema of all the tissues of the body. Yet the one is not the consequence of the other, and so we may see complete suppressions of urine without a degree of surface œdema that can be recognized clinically, or a generalized (toxic) œdema in which the eyes are swollen shut, the skin stretched and shining, the fingers and toes swollen until they stand apart, and yet no urinary findings; or such developing *after* the generalized œdema has persisted for days. The œdemas of the different organs are each to be sought for in turn and their intensity and importance judged alone from the point of view of the organ in which they occur. An œdema of the medulla (nausea, vomiting, CHEYNE-STOKES breathing) or brain (headache, stupor, coma, convulsions, delirium, "insanity") is more important than one of the kidney, and this than one of the liver. An œdema of the optic nerve is not dangerous to life, but, if persistent, destructive to vision. Many times the same degree of swelling in the skin has no lasting consequences.[1]

§ 6

The variations from the normal blood pressure bring much clinical light, but no quick statements regarding their meaning can safely be made. The kidneys may be almost or completely destroyed without the slightest increase in pressure. It may safely be said that the generalized parenchymatous nephritis due to a poison or to an infection of the kidney never alone increases the pressure. Early in some intoxications and infections there is a slight rise in blood pressure because of their effects upon the circulatory system, but when they persist they almost always lead to a gradual decrease in blood pressure (ending in the general picture of toxic or toxemic shock). A heightened or even very high blood pressure may be observed in patients

[1] Exactly as the albumin content of the urine rises in œdema of the kidney (nephritis) the albumin content of the cerebro-spinal fluid rises in œdema of the brain or cord. EDMUND M. BAEHR first called my attention to the high protein content of the spinal puncture fluid in three "uremia" cases. The care necessary to avoid the trap of a wrong diagnosis of brain syphilis on the basis of such findings is self-apparent.

having parenchymatous nephritis, but not because of this. The pressure is nearly always the expression of brain œdema. *An increasing or high blood pressure in the intoxication of pregnancy, for example, points not to kidney disease, but to a developing brain œdema due to the same poisoning which is producing such kidney signs as may be present.*

Except for such causes of high blood pressure as these in patients showing abnormal urinary findings, a high blood pressure is most commonly due to blood vessel disease or certain types of heart lesions. Of the two, blood vessel disease is, of course, the commoner offender. A high blood pressure with cardiac enlargement, a few casts and albumin, when an old primary heart lesion can be ruled out, calls for a primary diagnosis of vascular disease. The maintained high blood pressure in such patients is not in itself to be regarded as a bad sign,—it may mean a well-marked vascular involvement, but it also means good heart muscle. After the accidental variations due to work, excitement, etc., have been taken into consideration, a rising blood pressure usually means progress of the vascular disease or development of a brain œdema. A falling blood pressure is good when we can trace it to improvement in the vascular disease, but when such is not there, it becomes too often the sign of a failing heart muscle. It should also be remembered that a high systolic pressure alone, while it means a good heart muscle, does not yet mean an effective circulation of the blood. The diastolic blood pressure must be correspondingly high. A low diastolic blood pressure means that the effect of the systole in moving the blood forward is being largely lost, and the finding of an aortic leak or a dilating heart too commonly explains why it exists.[1]

These considerations render it clear why, in the so-called chronic interstitial types of nephritis, therapy should be directed primarily toward the relief of the blood vessel condition so far as such may be possible, and toward the maintenance of an effective heart action. To relieve the symptoms of the patient and to reduce the blood pressure, persistent, daily administration of sufficient alkali to keep the urine constantly neutral is undoubtedly the most effective single thing we can do. Arthur D. Dunn came to this same conclusion entirely independently.

[1] See in this connection the interesting studies of Willard J. Stone: Jour. Am. Med. Assoc., **61**, 1256 (1913); Lancet-Clinic, **111**, 247 (1914).

It is remarkable how the high blood pressure will fall and remain low. As attempts to meet the vascular disease itself may be listed (because of my belief in its infectious origin) the approved hygienic means generally considered effective in combating such, as fresh air, rest, and good food, or when syphilis is suspected, iodids, mercury and arsenic preparations in addition. To bring aid to a distressed heart the use of digitalis and other cardiac stimulants, even though they raise the blood pressure, have long been known to be of service. Such therapeutic measures yield better results than the drastic dietary restrictions or the empirical incantations so often invoked over this long-suffering group of patients.

It is apparent also why measures which merely reduce blood pressure (except in cases of hemorrhage) are not only disappointing in their results, but may actually do harm.[1] I have several times seen alarming falls in the urinary output and once a complete suppression of urine with death of the patient eight days later after the administration of nitrites to reduce blood pressure in cases of chronic interstitial nephritis associated with vascular disease. Suppression of urine is bound to follow the lack of blood supply thus induced to kidneys which are already barely getting enough with a high blood pressure. There is no justification for giving nitrites in chronic interstitial nephritis unless we can show that while reducing general blood pressure we are not at the same time reducing the blood supply to the kidney to a dangerous point.

And yet these considerations must not be interpreted as an interdiction of the use of nitrites in all clinical conditions. When we deal with symptoms referable to vascular disease or "vascular spasm" affecting particularly but one organ, as in angina pectoris, the nitrites may well be tried in the hope of obtaining a vasodilatation in the affected organ without losing enough in other organs to do harm. But whether we will or will not get such an overplus of good effects can be determined only

[1] D. M. Ervin (Jour. Am. Med. Assoc., **70**, 1208 (1918)) found that the administration of blood pressure lowering drugs (nitroglycerin) in patients brought into the hospital in convulsions, precipitated new attacks, while the administration of blood pressure raising drugs (epinephrin) prevented such. Ervin holds that the convulsion comes on whenever the blood pressure falls below the intracranial pressure. Proper treatment, obviously, should try to reduce the intracranial pressure.

by careful observation of the individual patient when such vasodilators are first tried.

§ 7

We should not fail in looking for the factors capable of producing the acid and similarly acting substances which we hold to be directly responsible for the development of the signs and symptoms of a nephritis to consider foci of infection.

After we have eliminated cold, hard work, heart disease, the poisonous products of pregnancy, bichlorid of mercury, arsenic, etc., as the possible first causes of a nephritis, the infections loom up as the next most important factors, especially in the more persistent forms of this disease. The parenchymatous nephritides that do not clear after bedrest, alkalinization and a liberal diet (like the pregnancy intoxications that do not clear with proper treatment five to ten days after delivery) or the spotty types (either the infectious nephritides in children or adults or the vascular types in maturer individuals) which show signs of getting worse should all be examined and with the greatest care for points of infection. The practitioner (and the specialist as well) should learn that in this field *negative findings do not count.* Disease is never "idiopathic" and it does not progress without cause. Our own abilities may be inadequate to discover them but that these things have beginnings and that their first causes have not been eliminated if they show signs of progressing—of this there can be no doubt. Hence the importance of searching for foci of infection in the tonsils, teeth, ears, and mastoids; in the sinuses of the head and face; in the genito-urinary tract of men and women, as well as elsewhere in the body. The causal connection between such points of infection and the signs and symptoms of a nephritis with its alleged consequences is often brilliantly demonstrated by the clearing up of long-standing cases of albuminuria, by a persistent fall in a long standing high blood pressure, by an improved general circulation, by a disappearance of "uremic" headaches, etc. How comparatively trivial and constantly neglected foci of infection lead to toxic and destructive changes in many of the organs of the body (including the kidney) has been beautifully demonstrated by the clinical, bacteriological and experimental studies of the Chicago school (Frank Billings, Edward C. Rosenow, E. R. Le Count, Rollin T.

Woodyatt, D. J. Davis, Ernest E. Irons, Wilber E. Post and their collaborators).[1]

§ 8

The above remarks may serve, I trust, to make it clear that what is of importance to the victim of "chronic Bright's disease" is not his vibration between no albumin and a fraction of a gram to the liter of urine, but the general estimate of the progressiveness or non-progressiveness of his disease with time and under the influence of the advice of his regular, medical father confessor. Recourse to Latin terminology, bedside debate of the importance of "coefficients" (the nature of which is hardly understood by the authors who produced them), the hash of fact and fancy which those of us who have authority pass off as "science"—these things mean nothing to a patient and nothing to the physician who must care for him for months or years after we have had him a week. The value of any therapy in "Bright's disease" has been judged too much from a few badly made and ultra-refined analyses of the urine while a patient was spending ten days with us in a city hospital. What we really want to know is how good the therapy is when the patient is spending ten years with his doctor at work in the country.

With these facts in mind, which show how the whole patient and not only his kidneys must be seen if we would judge rightly

[1] To the long list of "metabolic" diseases already eliminated by these workers we must, I think, add gout. In five patients—4 men and 1 woman—falling strictly within the text-book type of the disease (nocturnal big toe attacks, urate tophi in ears and skin, unsymmetrical urate deposits in finger joints, susceptibility to nucleo-protein feeding, etc.) badly infected teeth were observed in all. Two have recovered absolutely since losing all their teeth. A third who would develop "gouty" attacks whenever his teeth were "cleaned" by a dentist is better. The remaining two still have their teeth—and their gout. May we not better regard these patients as suffering from embolic infectious arthritis with the urate deposits secondary thereto and analogous to the formation of "stones" in infected gall bladders, kidneys or urinary bladders? The same infectious embolism in other organs will then explain the alleged consequences of gout, as the occasional fever, the muscular involvement, the nephritis, the occasional leucocytosis, etc. We are only slowly beginning to learn the multiplicity of pathological effects exerted by one and the same organism when grown under different environments. See in this connection the fundamental work of William B. Wherry: Jour. Inf. Dis., **2**, 436 (1905), cholera red reaction; Arch. f. Protistenkunde, **30**, 77 (1913), flagellation of amebae; Centrabl. f. Bakt., Parasitenk. u. Infektionskr., **70**, 115 (1913), "spore" formation in tubercle bacilli; Jour. Inf. Dis., **13**, 114 (1913), acid proofness in tubercle bacilli.

the meaning of his urinary findings, we shall consider next the meaning and value of some methods which have been resorted to by way of determining kidney efficiency.

2. Underlying Principles and Clinical Value of Kidney Efficiency Tests

Clinicians have for many years and in many ingenious ways tried to determine the physiological efficiency of different organs. How valuable would be at times a correct knowledge of the working power of the heart, of the chemical activity of the liver, of the secretory activity of a kidney is, of course, obvious, and yet the bitterness of controversy which surrounds the various attempts that have been made to estimate such scientifically suffices to indicate how far we are still from the desired goal. Before my own position in the matter, so far as the kidney is concerned, is expressed, I would emphasize the necessity of bearing in mind some physiological truths, the ignoring of which has led to the expectation of obtaining by efficiency tests on different organs impossible ends, or to a condemnation of such as have real, even though rather limited, value.

With the exception of certain portions of our central nervous system it is characteristic of our organs that they each contain several times as much material as is necessary to meet the work requirements of every day. Seven-eighths of our pancreas may become functionless and still enough internal secretion be obtained to keep us from becoming diabetic; the work demands on the heart may be trebled or quadrupled and yet it goes on; half or three-quarters of the liver may be destroyed with no signs of a hepatic insufficiency. Similar claims may be made for each of the organs of the body. We possess, in other words, a potential power many times that actually used.

The important corollary of this fact is that *an organ continues to show a normal function as long as more than such a physiologically necessary minimum remains preserved,* even though large pieces of it may actually be temporarily functionless or totally destroyed. The more definitely more than such a physiological minimum is still preserved the less can any ordinary test give us an inkling of the actual amount of damage. The test has to be heightened *to the point of straining* all of the normal

or imagined remnants of an organ before a defect here will manifest itself. These considerations hold for the functional testing of all organs. How they apply to the specific problem of the kidneys is evident from what follows.

The mystic element of human nature is well expressed in its so commonly voiced faith that it is the function of the kidneys to excrete the poisons produced in the body. Such a view ignores the fact that they are quite as likely to be excreting substances for a lack of which the animal is perishing, as when in salt starvation they continue to secrete this even though its lack in the body is killing the animal. But however we may choose to look upon such obvious facts, it is evident that *the kidney's ability to give off dissolved substances may serve as one type of kidney efficiency test.* To most this has appeared the only test, and yet we need but recall that a dry kidney can get rid of nothing at all to show how its ability *to give off water is really quite as important, in fact, as previously emphasized,*[1] *it is the primary function of the kidney, and the secretion of all dissolved substances is secondary to this.* The efficiency of a kidney may therefore be gauged by its ability to secrete water. Before discussing the utilization of these considerations in clinical practice, some animal experiments in which we have conditions under better control than in our clinical practice had best be borne in mind.

The best way to do away with any amount of organ function is to remove parts of the organ. In the case of the kidneys it is an easy matter to take away three-fourths and even more of the total substance and yet have the animal live. Such removal means, of course, a loss of three-quarters of the normal kidney function. *Animals so operated upon excrete water and all dissolved substances, such as the various dyes, exactly as do normal animals.* Even excessive amounts of water given such animals by way of placing "strain" on the remaining portion are easily cared for. The important conclusion to be drawn from this is that *mere loss of three-quarters of the normal kidney function* (and even more) does not yet betray itself to any of our ordinary functional tests. This fact is of great clinical importance because it means that ordinary efficiency tests tell us nothing until we are working on the last quarter or less of our total kidney efficiency. Efficiency tests, as we shall see, still retain a useful purpose in

[1] See page 368.

spite of this, though it might as well be emphasized now that when we are thus working on the last elements of a still functioning kidney obvious clinical signs will in most cases tell us quite as much.

It is well now to re-emphasize that the secretion of dissolved substances is secondary to the secretion of water, not in the sense that if a liter of urine brings out a gram of dissolved substance two liters will bring out two, but in the physico-chemical sense [1] that if no water at all is secreted into the uriniferous tubules no dissolved substance at all can be washed out of the kidney parenchyma and therefore none be secreted. If some water comes through then some dye comes out also, while with more water more dye will be washed along. But the *time* that the water remains in contact with the parenchyma plays an important part in permitting diffusion, etc., wherefore the concentration of the dye may be greater with less urine than with more, but other conditions the same, the *absolute* amount never.

The increased output of any dissolved substance when, other conditions remaining the same, the amount of water passing through the kidneys is increased, has for half a century been one of the well established facts of physiology. Experimenting upon himself C. GENTH,[2] for example, found that during a control period he voided a daily average of 1252 cc. of urine with 40.2 grams of urea. In a subsequent period when everything was kept constant except that an added two liters of water were consumed he secreted 3250 cc. of urine with 46.6 grams of urea. When the water intake was increased to four liters the urine rose to 5500 cc. and the urea to 54.2 grams. Similar results are obtained if the observation periods are measured by hours instead of days.[3] While such increases have been quite generally attributed to an increased "protein metabolism," they probably represent pure washing-out processes, for upon return to the original water intake the urea excretion falls not only to the normal, but for a period to a figure even below this. What has been said here of urea holds also for the total urinary nitrogen or

[1] See pages 206, 367 and 640.

[2] C. GENTH: Ueber den Einfluss des Wassertrinkens auf den Stoffwechsel, Wiesbaden (1856).

[3] OPPENHEIM: Pflüger's Arch., **23**, 465 (1880); see also NEUMANN: Arch. f. Hyg., **36**, 248 (1899).

some of its other fractions, as ammonia, creatin,[1] creatinin, and alantoin.[2] It holds also for such salts as sodium chlorid.[3]

The whole matter is easily demonstrated on animals with normal or reduced kidney substance. With ordinary feeding, rabbits eliminate 55 to 70 per cent of a dye (1.5 milligram phenolsulphonephthalein) in the two hours following its introduction intramuscularly, but if the water secretion is heightened by intravenous injection of salt solution 65 to over 80 per cent will be obtained. While the concentration in the individual samples of urine in the latter case is lower than in the former the absolute amount given off is not. With plenty of water coming through the kidney the dye also appears earlier than when such is not the case. Exactly the same occurs in patients. With little water coming through the kidney the output of potassium iodid, of milk sugar, of sodium chlorid, of a dye, etc., is lower than when the same test is repeated on the same patient, but a heightened water secretion is assured by a greater water intake.

I have been told that J. Alberran first taught that a "polyuria" following the administration of water was the best evidence of a patient's kidney efficiency. Alberran's original communication is not accessible to me, but it expresses a view with which I heartily concur. I have never seen a patient showing a normal water secretion who did not also show a normal output of any of the dissolved substances customarily used in kidney tests.

To have a water, or any other type of kidney test mean anything, it is evident that all the factors outside the kidney which are capable of influencing it must be eliminated as far as possible. If, for example, we do not get a normal water response this does not at once mean that the kidneys are affected. The patient's body colloids may not have been previously saturated with water, or exercise may have temporarily increased their water-holding power, or a circulation may be so defective that the blood never becomes properly arterialized and so "free" water for urinary secretion appears only slowly in it.

To eliminate as many of these factors as possible it is necessary in making efficiency tests on a patient to put him at bed

[1] C. C. Fowler and P. B. Hawk: Jour. Exp. Med., **12**, 388 (1910).

[2] L. T. Fairhall and P. B. Hawk: Jour. Am. Chem., Soc. **34**, 546 (1912).

[3] S. A. Rulon and P. B. Hawk: Arch. Int. Med., **7**, 536 (1911).

rest for at least twenty-four hours and let him have an unrestricted diet. The best time to make a water test is two and one-half hours after breakfast or two hours after the last water was drunk. It takes a normal person about this time to eliminate whatever free water exists anywhere in his body. When this state has been attained, but not one beyond this in which the tissues are beginning to dry out, the patient empties his bladder (or if absolutely necessary a catheter may be inserted) and 500 cc. of drinking water are consumed. A normal person (or one having what will be called a normal kidney efficiency) excretes 400 to 500 cc. of the consumed water in the next two hours. The excretion shows an optimum point at the end of about an hour. The results of a few actual tests will show how the curves run.

TABLE CXXIX

URINARY OUTPUT IN CC.

Time in minutes and hours.	Normal.	Vascular disease with high blood pressure, cardiac hypertrophy, no heart murmurs, casts and albumin constantly in urine.		Infection of kidney (unknown type). Casts and polymorphonuclear leucocytes from the kidneys constantly in urine. Occasional slight rises in temperature. No abnormal findings in rest of body.	One kidney removed for infection. Remaining kidney has shown large numbers of casts, leucocytes and albumin for several years.
		Test 1	Test 2		
0					
.15	25	40	19	20	37
.30	50	48	31	31	43
.45	76	119	65	59	43
1.00	72	148	119	96	53
.15	62	51	128	92	59
.30	65	44	78	58	54
.45	57	34	47	25	49
2.00	28	26	29	23	42
Total...	435	510	518	405	380

A secretion of water above the total of the 500 cc. consumed is usually attributable to the fact that free water over and above that administered existed in the body at the time the test was started. If a patient consumes water against instructions, or if in the digestion of his food considerable amounts of water are freed, these quantities are, of course, added to the 500 cc. administered. Similarly, a low secretion does not at once mean an involvement of the last quarter of the total kidney substance.

It may simply mean that the patient was not saturated with water and calls for an immediate repetition of the test. As the first administration of water ordinarily suffices to saturate the body colloids the second test is usually more reliable than the first.

We need not specially emphasize that the outcome neither of the water test nor of any other functional test depends solely upon the functional ability of the kidney. A heart lesion, extensive interference with the respiration, etc., may all give rise to a deficient water output, and yet the kidney itself be but little affected. Neither do any of these tests tell us what is the pathological background for the disturbance in the kidney. They only tell us if the functional capacity has fallen below a certain minimum, regardless of the fact whether this disturbance is of a type which in a few hours will be removed, or is due to permanent destruction.

I make it a rule to use with the water test one of those in which the elimination of a dissolved substance is followed, and the well worked out phenolsulphonephthalein test of J. T. Geraghty and L. G. Rowntree [1] is perhaps the simplest and best of these. Geraghty and Rowntree provide for an adequate water secretion in their test in advance by having the patient consume several hundred cubic centimeters of it. While I lay greatest stress on the water secretion capacity of a kidney and have never found one which if it would eliminate water would not also eliminate a dissolved substance, the use of a dissolved substance capable of rapid elimination, as phenolsulphonephthalein, along with the water test furnishes a valuable check. If a kidney is functioning well, but the water elimination is low due to some accidental factor such as insufficient water consumption, the disproportionately higher elimination of the dye at once betrays the fact, for the dye is washed out of the kidney by very little water. The real significance of the low water excretion due to such accidental factors is therefore immediately disclosed.

A set of observations on the excretion of phenolsulphonephthalein and other dyes in experimentally induced nephritides, interesting because of their bearing on the interpretation of clinical findings, has recently been made by O. Schwarz.[2] He finds that

[1] J. T. Geraghty and L. G. Rowntree: Jour. Am. Med. Assoc., **57**, 811 (1911); **60**, 191 (1913); **61**, 939 (1913); Arch. Int. Med., **9**, 284 (1912).

[2] O. Schwarz: Pflüger's Arch., **153**, 87 (1913).

when the acid content of the body is increased (resulting, as we have previously seen, in a retention of water and a diminished urinary output with casts and albumin in the urine) phenolsulphonephthalein also fails to be excreted. Edward B. Reemelin and Raphael Isaacs [1] observed the same fact in dialysis experiments on blood. Blood serum holds fast to phenolsulphonephthalein when acids are added to it. Under similar circumstances the blood colloids also retain urea (non-protein nitrogen). In perfusion experiments on the kidney Isaacs [2] was able to show that lack of water secretion, reduction in phenolsulphonephthalein, chlorid and urea output, and appearance of albumin in such "urine" as was secreted all followed increase of the acid content of the perfusing liquid, while a reduction in this led to opposite results. The acid variations were, moreover, slight, all lying within the ranges observed " physiologically."

These findings are such as would be anticipated on the colloid-chemical basis. They teach at the same time how important are the extrarenal factors in determining secretion of water and dissolved substances from the kidney. Phenolsulphonephthalein, chlorids and urea are subject to the distribution law as are all other dissolved substances, and so under the influence of acid, salts, etc., are taken up or rejected by protoplasm elsewhere in the body as they are in the kidney.

Clinical parallels to these experimentally demonstrable facts are common. I need but state that in the acuter types of heart failure the excretion of phenolsulphonephthalein, urea ("non-protein nitrogen"), chlorids and water all drop at once, to rise again as soon as the heart recovers. Here the whole body, and incidentally the kidney, is suffering from a lack of oxygen with its accompanying abnormal production and accumulation of acid. How much more important it is in this illustration to recognize the heart lesion than the incidental kidney involvement needs no emphasis. Schwarz has, moreover, brought experimental proof of what was predicted theoretically. After acid injection (with its accompanying nephritis) some dyes are excreted even *better* than normally.[3]

[1] Edward B. Reemelin and Raphael Isaacs: Am. Jour. Physiol., **42**, 163 (1916).

[2] Raphael Isaacs: Am. Jour. Physiol., **45**, 71 (1917).

[3] See page 640.

If these considerations are borne in mind it will serve to explain why I hold that *the best evidence of kidney efficiency is its ability to excrete water. A kidney capable of secreting water is secreting in proper fashion everything else, and as long as sufficient water is supplied the patient and comes through, his state is not to be attributed to defective kidney elimination.* This is true even of the alleged "uremias" encountered in chronic interstitial nephritis. *The ability of a kidney to put out water may safely be used as an index to the amount of kidney substance not involved in a pathological disturbance; the number of casts and amount of albumin as an index to the amount thus involved.*

The use of dyes in testing kidney efficiency finds its greatest service, perhaps, in dealing with one-sided kidney lesions. While ureteral catheterization will give us the water output from each of the two kidneys it is not devoid of danger. Cystoscopic observation of a *properly chosen* dye coming freely from one ureteral opening while little or none of it is coming from the other often suffices to betray the almost functionless character of one of the kidneys.

The use which may be made of functional tests is self-evident. They are neither to be condemned as universally as they have been by some writers, nor yet to be regarded as alone capable of giving a correct index of the state of the kidney, as assumed by others. Except in one-sided kidney lesions where it is important to determine, as before surgical interference, the functional capacity of the kidney to be left, very evident clinical symptoms usually suffice to let us know when we are working on the last quarter (or eighth) of our total normal kidney capacity. When with adequate water supply by mouth a kidney secretion remains persistently low, mere measurement and examination of the twenty-four hour output suffice to tell us of the state of the kidneys, and functional tests will not add much. The claims of some authors who have felt it possible to predict the onset of "uremic" attacks and death in patients with chronic interstitial types of nephritis from their low output of some dissolved substance through the kidney need to be restudied. As previously emphasized, animals and patients deprived of their kidneys do not die as do those which clinically we diagnose "uremic." These "uremic" deaths are due to œdemas of the brain, and such are secondary, not to loss of kidney function, but to vascular

disease, to thromboses of the cerebral vessels, and to hemorrhage. Patients with chronic interstitial nephritis associated with blood-vessel disease die once in three times of a failing heart. And since individuals with uncompensated heart lesions fail to excrete water and dissolved substances exactly as do such as have their kidneys primarily involved, it may well happen that death is correctly prognosticated in such from a low dye output, but, to repeat, the death is again not due primarily to kidney disease, but to cardiac involvement.

3. On Acidity Measurements of the Urine

Such stress has been laid upon the importance of an abnormal production and accumulation of acid in various organs of the body in giving rise to an œdema in them, or in the case of the kidney, in leading to the development of the signs of a nephritis, that the question naturally arises whether we cannot in some way measure this acid content by way of getting an index to the severity of the changes occurring there. We have not at present any methods which can be used *clinically* for measuring changes in the acid content of the different organs in the body. Various attempts have been made to measure the acidity of the blood and these all show that in œdema and nephritis it is increased. The findings are, however, open to much question.[1] Reliable data on the acidity of the different *secretions* from the body, as the urine, the saliva and the sweat are, however, at hand, and other things remaining the same, the laws of chemical equilibrium then permit us—from the acidity changes in these secretions—to conclude that there must have been similar changes in the tissues from which they came. Thus an increase in the acidity of the urine means, generally speaking, an increase in the acid content of the kidney from which it came, and vice versa. By following the changes in acidity of some or all of the secretions from the body we may therefore obtain valuable clinical suggestions as to the severity of an acid intoxication in the body and an index to the efficacy of treatment with alkalies, etc.

[1] See the next section, page 775.

§ 1

We have first to say exactly what we mean by urinary "acidity." In the days before physical chemistry the acidity or the degree of acidity of such a secretion as urine was usually measured by titrating it with an alkali of known strength. This gives the so-called *titration acidity* of the liquid, and this type of analysis has been applied to the urine, as to many other fluids derived from the body. The titration acidity of the urine in nephritis has by scores of investigators been found to run much above that of normal urine and we may still use it to advantage in studying our clinical cases to-day. A titration which for clinical purposes is sufficiently accurate, can easily be made by adding to 25 cc. of the urinary sample one or two drops of a 0.5 per cent solution of phenolphthalein in 50 per cent alcohol and then titrating with one-tenth normal sodium hydroxid until a permanently pink color is obtained. While the capacity of the urine for thus neutralizing alkali varies throughout the twenty-four hours (being lowest just after meals and highest before meals, after exercise and through the night) *normal urines, when mixed, twenty-four hour specimens are compared do not take up more than 20 to 30 cc. of one-tenth normal sodium hydroxid per 100 cc. of urine.* It must at once be clearly understood, however, that *this titration acidity of the urine is not an absolute guide to the degree of acid intoxication occurring in a kidney.* The reasons for this are obvious. When, for example, we compare the poisonous effects upon the tissues of equivalent concentrations of phosphoric acid, ammonium dihydrogen phosphate, diammonium hydrogen phosphate, and triammonium phosphate, the first is found to be highly poisonous, the second more mildly so, and the third and fourth still less poisonous, in the order named. Yet the titration acidities of all four *as ordinarily determined* by titrating with standard sodium hydroxid solution give the same reading. These facts must be kept in mind when judging the clinical significance of the titration acidity of the urine. For, clearly, were a urine filled with pure, highly poisonous phosphoric acid instead of the comparatively innocuous dibasic or tribasic salt, the titration acidity would not betray this fact.

Determination of the titration acidity is nevertheless of great value if what has been said be kept in mind. It is capable of

giving us definite evidence of the existence of an abnormally high acid content in the urine (and therefore in the kidney) and of the changes in this from hour to hour or day to day. The trouble is that in actual clinical practice titration methods are scarcely used, or when used they are not employed often enough to give any adequate check on the short period variations in the chemical state of the patient. This is, of course, because titrations take time—more time than is ordinarily at the disposal of the practicing physician. Titration acidity does not, however, vary *directly* as the degree of intoxication, and only ignorance of the elementary facts of chemistry would ever lead anyone to expect such complete parallelism.

§ 2

The physical chemists have more recently distinguished between the latent and the active acidities of a fluid, meaning by the first the total replaceable hydrogen, by the second the hydrogen ions yielded upon solution in water. When the physical chemists speak of acidity they usually refer to the active or *hydrogen ion acidity*, and a large portion of them believe that all so-called acid effects are dependent exclusively upon the presence and the number of these hydrogen ions. When the acid content of a system is increased there follows usually an increase in the hydrogen ion acidity. Increasing the amount of acid in a beaker of water is followed by an increase in the number of hydrogen ions, and when we deal with very dilute solutions the increase in hydrogen ion acidity is very nearly proportional to the increase in the amount of acid. It is for this reason that the hydrogen ion acidity of urine coming from a kidney containing a more than usual amount of acid, as in nephritis, is usually increased. The increased acid content of the kidney, to satisfy the laws of chemical equilibrium, demands an increased acid content in the urine coming from it, and as an expression of this we find an increased hydrogen ion acidity. The hydrogen ion acidity of the urine can be measured in various ways, and since some of these can be used clinically it constitutes *one* figure of value in judging a kidney case.

It must, however, be clearly understood from the outset that hydrogen ion acidity determinations of the urine can alone be no absolute index to the severity of the intoxication occurring in the kid-

ney, nor yet that every increase or decrease in hydrogen ion acidity is or must be followed by a corresponding increase or decrease in the severity of the intoxication in the kidney. The reasons for this are, of course, perfectly obvious. The attempt was made some twenty years ago to show that the toxicity of various acids, as determined by their effects upon growing plants, the sense of taste, the absorption of water by muscle, the aggregation of infusoria, etc., followed their degree of ionic dissociation. It was early learned, however, that no such parallelism exists. Thus, it was found that acetic and other organic acids with their low dissociation produced physiologically as great effects as the highly dissociated hydrochloric, nitric, and other acids. On the other hand, the rather highly dissociated sulphuric acid produced physiological effects far below the weakly dissociated organic acids. In other words, *physiological effect is not determined solely or even in the main by the degree of dissociation.* I believe I was the first to show that an entirely similar disproportion between degree of ionic dissociation and effect produced holds for the swelling of various protein colloids, and in so doing emphasized that the observed physiological reactions depend, in the main, upon the protein constituents of the tissues under consideration.

It would, therefore, have been manifestly absurd for me ever to have claimed that any physiological effect could be measured by merely determining quantitatively the hydrogen ion acidity, and this whether we deal with purely physiological reactions or with the question of the development of the signs of a nephritis in a kidney. An increase in the hydrogen ion acidity of the urine above a normal standard may serve as evidence of an abnormal acid content in the kidney itself, but it can never be a complete measure of the degree of the intoxication. To make the matter more concrete we need but illustrate this by saying that on poisoning a kidney with hydrochloric acid there occurs a great increase in the hydrogen ion acidity of the urine, yet if we produce a similarly great intoxication by the use of lactic acid only a slight rise is observed; on the other hand, intoxication with sulphuric acid again gives us a great rise in hydrogen ion acidity, and yet comparatively little effect on the kidney.

To these considerations needs to be added the further fact, which I have so often emphasized, that an increase in the acid

content in such an organ as the kidney does not alone determine the degree of effect produced. The presence and kind of salts found in a protein influence markedly its swelling and solution, and mere measurement of the hydrogen ions in the urine tells us nothing of these factors. As a matter of fact, the addition of salt (even of neutral salt) to an acid protein mixture brings about an actual rise in hydrogen ion acidity of the liquid about the protein as this shrinks. The same fact can at times be observed clinically when a temporary *rise* in the hydrogen ion acidity of the urine follows the active administration of salt alone. Unless such simple principles of physical and colloid chemistry be borne in mind we shall never come to a correct understanding of the value and limitations of such hydrogen ion determinations.[1]

[1] By ignoring what I have written here and in my previous books and papers L. J. HENDERSON and his co-workers, W. W. PALMER and L. H. NEWBURGH, have wasted energy in attempts to disprove what I have never said. My constantly reiterated claim that certain changes in tissues are due to an "increased acid content" cannot at will be made to read by these authors an "increased (hydrogen ion) acidity." The latter may under otherwise constant conditions become evidence of the former, but the reverse need not follow. Thus, the generally higher hydrogen ion acidity of a tissue or of a fluid coming from that tissue is evidence of an increased acid content in the tissue, but considerable quantities of either acid (or alkali) may be introduced into any of our tissues, thereby raising their "acid content" even to the point of killing them, without any appreciable increase in the hydrogen ion acidity. When we add acid to a protein in the presence of an indicator the "acid content" of the protein rises from the moment we begin adding acid, but a long time may elapse and much may be added before the hydrogen ion acidity changes, as evidenced by a change in the color of the indicator. Would HENDERSON and his school hold that because the indicator had not turned no acid had yet been added?

Beyond this the findings of HENDERSON and his co-workers do nothing but corroborate my own teachings. While in his first communication HENDERSON thought his results to dispose of my views entirely, his more recent conclusions are less sweeping. Thus, he finds "The mean acidity in cardio-renal cases is undoubtedly high . . . which other observations lead us to consider a form of acidosis" (Jour. Biol. Chem., **13**, 404 (1913)). "This lack of response to alkali occurred most frequently in patients with kidney disease" (Arch. Int. Med., **12**, 163 (1913)). "The hydrogen ion concentration from individuals with severe cardiac decompensation is higher than normal" and "the hydrogen ion acidity follows the general clinical course, becoming normal when compensation is restored" (Arch. Int. Med., **12**, 146 (1913)). These conclusions sound strangely like my own. In the former of these articles HENDERSON advises against unchecked use of alkali in treatment because in too high concentrations it leads to albuminuria. This is a fact I emphasized long ago, but why is HENDERSON so willing to concede the albuminuria to be due to excessive alkali when he

Of the methods that have been or may be used to measure the hydrogen ion acidity of the urine (or any other body fluid) nearly all are too complicated for routine clinical use. Those of S. P. L. Sörenson and of L. J. Henderson are among the simplest,

strains so over the analogous behavior of acid? Of course, Newburgh, Palmer and Henderson found that "it could not be shown that there was any definite relation between hydrogen ion concentration of the urine and œdema in the cases studied" (Arch. Int. Med., **12**, 146 (1913)). But then, as pointed out above, we learned in the late nineties that physiological effect is nowhere proportional to the hydrogen ion concentration.

So far as the general biological views of Henderson are concerned he errs in these, as do most of the physical chemists working in biology. While I doubt not that the maintenance of neutrality in the organism is in good measure dependent on a play between monobasic and dibasic salts, some caution is necessary before all the conclusions of the physical chemists obtained on dilute aqueous solutions are bodily heaped upon protoplasm. Protoplasm is not a sack of water with a few salts dissolved in it. The water of protoplasm is hydration water and the dissolved substances are by no means all in simple solution. Not until it is shown that reactions occurring in gels are identical with those occurring in pure water—which we already know is not the case, for, as Findlay and Creighton (Biochem. Jour., **5**, 294 (1911)) have shown, so simple a phenomenon as the solubility of oxygen in serum is only one-fifth as great as that in water—can we continue to apply without modification to protoplasm the physico-chemical laws governing reactions in dilute watery solutions.

The latest criticisms of Henderson, Palmer and Newburgh (Jour. Pharm. and Exp. Therap., **5**, 449 (1914)), upon which the Journal of the American Medical Association lays great stress editorially (Jour. Am. Med. Assoc., **62**, 2033 (1914), are equally inconclusive. Must it be reiterated that all salts, and particularly the phosphates and acetates used by Henderson, Palmer and Newburgh as they were used by Max Koppel (Deut. Arch. f. klin. Med., **112**, 594 (1913)) even earlier—decrease and may suppress completely the swelling of proteins no matter what hydrogen ion concentration surrounds them? Since gelatin and fibrin show increased swelling even in the lowest concentrations of carbonic acid it is not true that "no influence to increase colloid swelling has ever been observed through the action of hydrogen ions varying within the ranges of acidity known to occur in the body or in the urine." Further, it has never been maintained that laboratory gelatin or fibrin was at once to be made identical with the proteins in our body. The body proteins are far more sensitive to acids, alkalies and salts than the long-suffering and mutilated materials we have salted and boiled out of them. The variations in the "acidity" of the blood noted by these authors are incorrectly maintained by them to be of no significance, for the fact remains that such as accompany mere change from arterial to venous blood already make the corpuscles hold 15 per cent more water, and if there is a passive congestion, 30. The clinician bases a diagnosis of œdema on a much smaller increase in general body weight than this. The arguments on the significance of "osmotic pressure" in water absorption by protoplasm may be referred back to the biologists who gave up the kind restated by Henderson, Palmer and Newburgh ten and twenty years ago.

but even these require more time and skill than is always available. A series of phosphate or acetate mixtures having a known hydrogen ion acidity are first prepared to which indicators (dyes) are then added. The urines properly diluted and containing the same indicators are then matched against the colors in the standard mixtures. The method has yielded valuable figures, but it is too complicated to find universal employment, and the degree of accuracy attained is, after all, not necessary for good judgment in medical practice.

To get a method which would yield for clinical purposes sufficiently accurate data and still be simple enough to be employed by anyone, I have made use of graded indicators such as the physical chemists use.[1] By using a number of dyes which show color changes at definite hydrogen ion concentrations and then using the same indicators on the urine it is possible to determine its hydrogen ion acidity. The indicators are so chosen that their turning points vary from each other approximately by the

Name of indicator and method of preparing same.	Concentration of hydrogen ions when indicator changes color.	Color of indicator.	
		In acid solution.	In alkaline solution.
Methyl orange (0.5 gram in 100 cc. distilled water)	10^{-4}	Salmon pink	Orange-yellow
Paranitrophenol (2 grams in 100 cc. alcohol)	10^{-5}	Colorless	Greenish-yellow
Sive's red [1] (2 grams in 100 cc. water)	10^{-5} to -6	Red	Canary yellow
Methyl red (0.2 gram in 100 cc. alcohol)	10^{-6}	Magenta red	Canary yellow
Rosolic acid (0.5 gram. in 50 cc. alcohol +50 cc. water)	10^{-7}	Orange-yellow	Magenta
Phenolphthalein (1 gram in 100 cc. alcohol)	10^{-9}	Colorless	Bluish-red
Thymolphthalein (0.5 gram in 100 cc. alcohol)	10^{-11}	Colorless	Blue

[1] This is the hydrochlorid of paramonomethylaminoazobenzeneorthocarbonic acid. It does not turn until a hydrogen ion acidity higher than that necesary to turn methyl red is attained, and yet shows an acid reaction before such is discoverable with paranitrophenol. Under the direction of LAUDER W. JONES, B. SIVE worked this out to meet the need for an indicator lying between these points.

[1] See ARTHUR A. NOYES: Jour. Am. Chem. Soc., **32**, 815 (1910), where is given an excellent discussion of the whole question of measurement of hydrogen ion acidity. See also EDUARD SALM: Zeitschr. f. physik. Chem., **57**, 471 (1907). FRITZ GLASER: Indikatoren, Wiesbaden (1901); S. P. L. SÖRENSEN: Biochem. Zeitschr., **21**, 131 (1909); L. J. HENDERSON: Biochem. Zeitschr., **24**, 40 (1910); W. M. CLARK: Determination of Hydrogen Ions, Baltimore (1920).

power of ten. Of the many indicators which might be used those are best which do not give colloid precipitates when added to urine. The preceding series (see table on page 771), the end points of which are sharp and can be readily recognized even in highly colored urine, have given excellent results in my hands.

In practice 10 cc. of urine are placed in a clean vessel (preferably a porcelain dish, which if distilled water is not available is first rinsed in the urine to be tested) and two drops of one of the indicators is then added to it. By trying successive indicators one is finally found toward which the urine is neutral. The urine has then the hydrogen ion concentration represented by the turning point of that indicator. As the acidity of the urine runs up, it will, of course, show an acid reaction to the upper members of the list, and as it runs down, to the lower. The turning point of the commonly used litmus is about that of rosolic acid. Urine not acid to phenolphthalein is alkaline to litmus, while thymolphthalein still remains colorless in urines which are distinctly alkaline to litmus.

As is to be expected, the hydrogen ion acidity of the urine shows great variations even in health. A man doing muscular work, or on a predominantly meat diet shows a higher acidity than one in bed or on a predominantly vegetable diet. The urine after meals is less acid than that before meals, and the night and early morning urines are more highly acid than those obtained after breakfast. The measurement of the hydrogen ion acidity of the urine is one of the few tests in which averages and twenty-four samples give us *least* information, and one *less* valuable than isolated tests at frequent intervals. The reasons for this are obvious. An athlete starting with a urine alkaline to methyl red secretes one highly acid to this shortly after going to work. But the urine returns to the originally alkaline state after a short rest. In the period of observation the urine originally free of albumin and casts becomes rich in these and loses them again. Had we measured only the *average* acidity as obtained by mixing the three samples of urine we should never have discovered the acid wave and perhaps maintained that the hydrogen ion acidity never went above the normal, as do some of my critics. The same is true of the alleged "physiological" and orthostatic albuminurias. At bed rest the urine shows a degree of hydrogen ion acidity which

increases as the patient assumes the erect position (while albumin, casts, etc., appear at the same time) to fall again on resumption of the horizontal. Only many tests at frequent intervals will betray these constant changes.

What we are interested in particularly, therefore, are the *highest* acidities registered and *the length of time these remain active*. Other things being equal, it is these two factors which determine how much effect is going to be produced on the colloids of the kidney.

In practice, now, when will we say that our patient is not exceeding a safe hydrogen ion acidity of the urine? To get at this value I chose the highest hydrogen ion acidity registered by healthy men on a full diet at bed rest. Such individuals do not show a hydrogen ion acidity sufficient to turn methyl red to the acid side except, perhaps, in the night urines voided between two and seven in the morning. The urine of healthy individuals who are up and about and on a full diet is also alkaline to methyl red for most of each twenty-four hours, though for obvious reasons, muscular exercise, high meat and fat diets, etc., may increase these hydrogen ion acidities.

In actual practice, therefore, methyl red should be used as the routine indicator for all urines. Those which have an acidity for the major portion of each twenty-four hours, or always, above this point I consider abnormally acid. Figures below this point and down to the turning-point of litmus or phenolphthalein I consider normal. Phenolphthalein rarely shows an alkaline reaction (if ammoniacal decomposition of the urine is not present) unless alkali is being fed to the patient. When the urine becomes alkaline to thymolphthalein too large quantities of alkali are being given, and the possibility of getting an albuminuria due to alkali is at hand.

When methyl red is used in routine fashion on all patients it will be observed that a large number run constantly acid to this indicator. This serves to bring home how common are low-grade types of acid intoxication. The more acute and the protracted infections, starvation cases, diabetics, patients with cardiac and respiratory disease, and patients with generalized parenchymatous nephritis all show an abnormally high hydrogen ion acidity. In ambulatory patients with chronic interstitial nephritis secondary to vascular disease such an abnormal

acidity may, for obvious reasons, be lacking, even though casts and albumin be present in the urine. In the later stages of the disease, especially when the circulation is beginning to fail, a high hydrogen ion acidity is the rule. When the acidity of the urine lies constantly below the turning-point of methyl red, or when by the administration of alkali it can be made to do so and be kept there, it augurs well for the patient. On the other hand, *I cannot recall a single patient in whom it was difficult or impossible to hold the urinary acidity below that of the turning point of methyl red who did not die.*

The correlation between increase in the hydrogen ion acidity of the urine and the appearance of albumin and casts in it can be easily observed in athletes who voluntarily produce much acid, as well as in patients with orthostatic albuminuria, or in heart cases showing the first evidences of insufficiency. After exercise or on assumption of the erect position the acidity mounts from somewhere below the turning-point of methyl red to a place above, and if this is maintained for a little time casts and albumin are likely to appear. The more definitely neutral the urine before such added efforts, the longer does it take for the casts and albumin to appear.

If the facts outlined are borne in mind the simple methods of measuring the hydrogen ion acidity described here prove of much clinical use. They apprise us of the existence of low degrees of acid intoxication in patients in whom we do not ordinarily consider them. By recognizing and meeting them by dietary regulations and alkali, we increase the reserve of these patients against the effects of such further intoxication as may be due to infection, anesthesia, or the trauma of operation. Or, in the established case, a fall in the hydrogen ion acidity of the urine tells us that our therapy so far as alkalinizing the patient is concerned is of a successful type. Since the indicator method is exceedingly simple we can follow the patient's condition from hour to hour, an important fact when we deal with the acuter manifestations of nephritis and allied conditions. In cases of complete suppression, in other words, when there is no urine to tell us when we have succeeded in getting an adequate amount of alkali into our patient *the reaction of the saliva serves as a useful* guide. Ordinarily this is neutral to litmus paper, but it turns acid in various intoxications. Alkali should be

given until it again turns neutral or even slightly alkaline to this indicator.[1]

4. Limitations of Indicator Methods

Recent studies on the colloid chemistry of soaps and proteins and the behavior of such systems toward various indicators[2] serve to show the origin of the many erroneous deductions which have been made during the past years as the outgrowth of findings derived from the application of indicator methods to living cells and their secretions. Some remarks covering this matter, since they bear upon the questions discussed in this volume, are therefore necessary.

Since the tissues, including the blood and lymph, are colloid systems and since the water in them is held as hydration water, I have insisted for many years past that ordinary physico-chemical laws and methods as derived from study of the ordinary "dilute" solutions cannot be applied to them without due reserve. I learned this more than a decade ago when, to prove the increased acid content of the tissues in œdema and nephritis, I tried to determine the hydrogen ion acidity of the blood. While in the more extreme cases such an increased acid content readily reveals itself by an increased hydrogen ion acidity, lower and known grades of acid intoxication produced by experimental means frequently fail thus to declare themselves to indicator methods. This is especially true when working (as one should) with undiluted blood or blood plasma. The reason for this is now to be made plain.

When a "neutral" hydrophilic colloid like soap or body protein (produced in the former case by adding to a standard amount of fatty acid the chemically necessary equivalent of standard alkali, or, in the latter instance by adding to each other the necessary gram equivalents of amino (fatty) acid and alkali) the resultant mixture is either acid, neutral or alkaline to such an indicator as phenolphthalein, depending upon the concentration of the water in the system. For

[1] The ordinary litmus paper is well-nigh worthless. It should always be tested for its sensitiveness before dependence is placed upon it. Only the neutral litmus paper of reliable manufacturers has proved of service in my hands.

[2] Martin H. Fischer: Science, **49**, 615 (1919); Chem. Engineer, **27**, 271 (1919); see also Soaps and Proteins, New York (1920).

purposes of illustration may be chosen the behavior of a rather concentrated (molar) "solution" of sodium caseinate, potassium oleate or sodium oleate. Phenolphthalein added to such systems remains colorless as shown in the lower portions of the test tubes of Fig. 216. As soon, however, as water is added to these colorless mixtures all turn pink, and with increasing dilution, bright red.

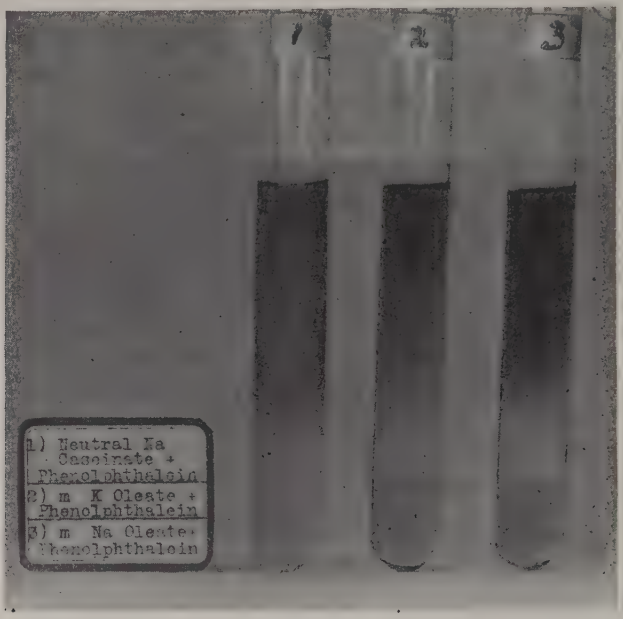


FIGURE 216.

What has been said of these sodium soaps and sodium caseinate is true, in general, of all the soaps and all the proteins, though the more striking behavior is shown by the soaps of the higher fatty acids or the basic compounds of the more complex proteins. An indicator (like phenolphthalein) added to a chemically neutral sodium palmitate or sodium stearate-water system (either a solid gel or a liquid mixture) turns the liquid portion of the system a bright red while the masses of soap (or other colloid) floating in this liquid remain pure white.

The common explanation of what happens in these instances is, of course, that of the physical chemists who assume that in the

concentrated soap "solution" there is little hydrolysis of the soap while in the more dilute one such hydrolysis is increased, and, sodium hydroxid being a stronger alkali than oleic acid is an acid, an indicator at once betrays the excess of hydroxyl ions.

Without listing the objections which may be raised against such an explanation (which at best accounts for but a small portion of what happens) it seems necessary to us, in order to get a more satisfactory interpretation of the whole picture, to call to mind the physical constitution of the lyophilic colloids as previously discussed in these pages, and, in the case of the soaps, to distinguish between the behavior of those portions of such systems which have the composition water-dissolved-in-soap and those which have the composition soap-dissolved-in-water. The two are totally different and while indicator methods may be used in an attempt to analyze the latter, they need not be (and are not) so applicable to the former. The so-called concentrated soap "solutions" are essentially solutions of the solvent in the soap, the more dilute ones systems of the opposite type and physicochemical methods and the laws governing dilute solutions may therefore be applied only to the latter. *The indicators may help for those portions of the system which are of the composition x-dissolved-in-water but they need tell us nothing of those portions composed of water-dissolved-in-x.*

The reactions in the solid tissues of the body (including for the most part those in the blood and lymph) are reactions in a medium analogous to a concentrated soap or protein-water system. The reactions, on the other hand, occurring in the watery secretions from the body (like the urine, saliva, gastric juice or sweat) are for the most part occurring in a system analogous to a diluted soap or protein. As the above facts have shown, indicator methods may be applied with a fair degree of accuracy only to the last named of these systems and yet it is the common practice of biochemists, biologists and clinicians to assume that protoplasm, too, is something analogous to a dilute solution.

The observations detailed above carry with them an interesting corollary. The color changes of indicators are in the majority of instances assumed to be dependent upon a play between the concentration of the electrically charged hydrogen and hydroxyl ions. If this assumption is held true for phenolphthalein (or for any other indicator which is held to act in this fashion) and especi-

ally if anyone maintains that such indicator methods may be applied to concentrated lyophilic colloid systems, then the conclusion is inevitable that *such concentrated systems contain no such ions.* The matter is of significance because living matter (normal protoplasm) behaves not as is so widely assumed, as water containing a little colloid but, more correctly, as a colloid containing some water. If this be true—and all experimental evidence supports such a conclusion—then *the material which we call living matter is probably under normal circumstances as electrically bland as is a concentrated soap solution,* a conclusion not to be overlooked in a day when the explanation of almost every fundamental life process is assumed to lie in an electrical notion of some kind. This criticism is not to be misunderstood. Differences in electrical potential, in ionization, etc., do come about in living matter, but they are more probably the results and the expression of injury to the involved structure than characteristic of the normal life of such.

It is well to emphasize also that only the *normal* cells are essentially systems of water-dissolved-in-protein. Indicators are therefore trickiest when applied to these systems. In disease the affected cells suffer changes which often are in the direction of "true" solution, in other words, the cells tend to develop into systems of the type, protoplasm-dissolved-in-water. Indicator methods become more reliable as this happens but *only for those portions of the cell which are of this "true" solution type.*

5. Ammonia Determinations, Acetone Compounds, "Acidosis," and Coma

In addition to measuring the titration or hydrogen ion acidity of the urine there is available another scheme of analysis which gives light regarding the existence and degree of acid intoxication within the body. The living animal labors constantly to keep as low as possible and to render as innocuous as possible the acids steadily produced in its normal or abnormal metabolism. It does this whenever possible by converting the products of its metabolism into carbonic acid, which may be lost from the body through respiration without simultaneous loss of an equivalent amount of alkali. All non-volatile acids such as sulphuric or phosphoric can be lost (through one of the secretions, like the urine) only by dragging along a minimal equivalent of alkali.

In many metabolic disturbances there is an interference with the normal production of carbonic acid, and then other, largely non-volatile acids, are produced in its place. These can be eliminated only in the form of salts produced through union with the bases of the body. When such abnormal production or accumulation of acid is not too intense, the reserve of bases in the body is usually sufficient to meet the need and the whole derangement comes and goes without disastrous effects upon the organism. But let the process be continued and this is not the case. In the herbivora the animal survives acid intoxication until its fixed alkali (the metallic bases) has been exhausted down to the physiological minimum. But in the carnivora (with which man is to be reckoned) a second source of base is available which, if it exists in the herbivora, is negligible in amount. When the fixed bases of the carnivora are heavily drawn upon these animals begin to produce ammonia and to use it to neutralize the acid. The carnivora can therefore withstand a continuous acid intoxication longer than can the herbivora.

In these simple considerations are embodied certain principles of analysis which have not yet found their deserved place in the practical handling of the nephritic. While they have long been used to advantage in diabetes and other metabolic disturbances they have been largely discarded in nephritis. The error of so doing will become apparent as we proceed.

Clearly, when an individual for any of a number of reasons becomes the subject of an intoxication with acid this may betray itself in the fluids coming from his body, as in the urine (feces, sweat, or saliva), not only by an increased titration or hydrogen ion acidity, but in either or both of the following two ways:

(*a*) By the appearance in it of acids which do not normally occur there, or

(*b*) By a relative or absolute increase in the amount of ammonia given off.

Many of the now available tests for the presence of diacetic and betaoxybutyric acids in the urine as well as for the related acetone can be quickly performed and are so simple as to be within the reach of the busiest practitioner.[1] The recogni-

[1] An excellent small guide thereto is S. W. Cole's Practical Physiological Chemistry, Cambridge (1913). See also Martin H. Fischer: Tice's Practice of Medicine, **1**, 423 (1920).

tion of lactic acid is also easy. As none of these or similar substances are found in appreciable amounts in normal urine their mere qualitative recognition becomes evidence for an abnormal body chemistry. *But it means no more than this.* One is not immediately to conclude that an "acidosis"[1] exists, if by this term is meant an intoxication with acid. An acetone body, lactic acid or any other normal or abnormal acid may be produced in great quantities in the organism and appear in the urine, yet if sufficient base is available they are neutralized and so are practically without effect. Even good men seem to forget this constantly. On the other hand, no acids of abnormal kind need be present in the urine (or elsewhere) and yet the organism be suffering from an intense degree of acid intoxication (as with phosphoric or sulphuric acids) if the available supply of base has been exhausted.

Since the normal amount of ammonia in the urine of an animal (like man) does not exceed a certain value, and since ammonia is not used to neutralize acid until the available fixed bases have first been heavily drawn upon, an absolute increase above the normal of the amount of ammonia in the urine becomes evidence of an acid intoxication. Furthermore, since the ammonia is formed at the expense of some of the other products of protein metabolism which escape in the urine, a *relative increase* in the amount of ammonia as compared with the total urea (or total nitrogen) of the urine is observed whenever an acid intoxication is under way, and becomes evidence for such.

As comparatively simple methods are now available for the quantitative estimation of ammonia and of urea (or total nitrogen) in the urine they are sure to find renewed application to many patients in whom an acid intoxication followed by nephritis is feared or existent. The considerations which led the older observers to discard such analyses as valueless depended

[1] The word "acidosis" has had its meaning twisted so greatly to suit the whims of different authors that it might well disappear from our medical and physiological writings. If it is used at all it must be used in its original sense as synonymous with "intoxication with acid." The mere finding of various abnormal acids or "acidosis compounds" in the urine or elsewhere does not yet mean an acid intoxication. The acetone bodies of a diabetic do not betray an acid intoxication, but an altered chemistry from which an acid intoxication may result.

upon the wrong interpretations which they made of their findings.

As is well known, routine examination of the urine of all patients reveals the fact that acetone, diacetic acid, betaoxybutyric acid, etc., occur in a large number of different clinical entities. Not only are they found in diabetes, but they occur in all types of general starvation, carbohydrate starvation, in many of the fevers (frequently in consequence of the bad feeding incident thereto), in cyclic vomiting, in certain of the so-called autointoxications, etc. Lactic acid, on the other hand, is found in uncompensated heart lesions, in severe anemias, in severe respiratory disease, in various intoxications, and in other conditions in which a lack of oxygen in some or all of the tissues of the body is in evidence. The finding of any or all of these abnormal constituents in the urine is evidence of an abnormal chemistry which may be followed by the signs and symptoms of a nephritis. Recognition of them in the urine is therefore a warning that the signs of a nephritis may supervene if care is not taken to feed properly (carbohydrate feeding) or to see that an adequate amount of alkali gets into the body to neutralize the acids. In the established nephritis the disappearance of these substances from the urine indicates that our therapy has been of an adequate and successful kind, a conclusion often brilliantly confirmed by the rapid disappearance of albumin and casts from the urine and of œdema from the body generally. I re-emphasize the necessity of keeping in mind that even large quantities of these abnormal substances may be found in the urine without any signs of nephritis, and conversely, that a severe nephritis may show but little of these substances or none at all. Thus, in diabetes large quantities of the acetone bodies may be found without the signs and symptoms of a nephritis, as long as an adequate amount of alkali is present to neutralize them. When the alkali becomes deficient the diabetic begins to show casts and albumin in the urine, to retain water (develop an œdema) and to have his brain affected in this general process (brain œdema and coma). Some of my critics seem constantly to forget these facts, as also that 40 per cent of all diabetics, especially those in the latter stages of the severer types of the disease, show casts and albumin.

What has been said of the diabetic (who really represents in

essence but a severe grade of carbohydrate starvation) is true, of course, of all who suffer from carbohydrate starvation from any cause whatsoever, as in cyclic vomiting, in the protracted fevers, in the starvations associated with gastric ulcer, malignant tumors, tuberculosis, etc. To judge properly of the actual degree of acid intoxication from which such patients are suffering we cannot rely solely upon the discovery of abnormal urinary constituents. A better index, as we have already emphasized, is found in the measurement of the titration and hydrogen ion acidities of the urine. To this we may add the quantitative estimation of ammonia in the urine and the determination of the ammonia coefficient.

For oft-emphasized reasons the ambulatory case of chronic interstitial nephritis associated with vascular disease need show no abnormal total ammonia excretion or abnormal ammonia coefficient (total ammonia divided by total urea or total nitrogen)[1] The dying spots of (parenchymatous) nephritis in the kidney need not produce enough acid to affect the mixed urine coming from the whole kidney. Such a patient has large amounts of normal kidney substance left, and as long as his heart and circulatory apparatus is not too heavily taxed he does not develop acid in sufficient amounts to call into play this ultimate neutralization mechanism of ammonia production. In fact, such a patient may die in coma (so-called "uremia") and yet show no increased ammonia output. This coma is, to my mind, an œdema of the brain, but since it is usually secondary to vascular disease the acid production is largely local and there is no reason why the body as a whole should show evidence of a general acid intoxication, to betray itself through an abnormal ammonia output in the urine. If the coma persists and the patient is not fed, or if convulsions supervene, the ammonia output is regularly found to rise. Because of this rise in ammonia output in the course of the coma it has been reasoned that the original "uremia" caused it and that the "uremia" itself cannot have been an acid intoxication of the brain (œdema of the brain). If what has just been said be borne in mind, it becomes readily intelligible how in the beginning there was an œdema of the brain (due to local acid intoxica-

[1] The figure obtained is practically the same, as normally, urea constitutes over 90 per cent of the total nitrogen.

tion) and how through this with its attendant bad feeding, etc., the patient's condition was made steadily worse.

An increased total and relative ammonia output is, as we should expect, particularly common in the so-called generalized parenchymatous types of nephritis, especially when protracted as in those incident to pregnancy. As a rule, these cases show with increase in albumin, casts, etc., or with increase in the generalized œdema, or with increase in the severity of the symptoms premonitory of coma and convulsions, an increase in either the total or the relative ammonia output. Where normally the ammonia coefficient does not exceed 5 or 6 per cent of the total urea or nitrogen (or in absolute amounts, 0.3 to 0.6 gram a day) such cases will show 10 per cent of ammonia or even more (with an absolute output of 2, 3 or even 4 grams a day).

These considerations suffice to indicate how important it is to follow the absolute and relative ammonia excretion in any case in which a nephritis is feared or existent. The value of such determinations in diabetes by way of foreseeing and forestalling coma has long been recognized. The coma incident to nephritis, like the coma of diabetes, is an œdema of the brain, and its appearance, particularly in the so-called generalized parenchymatous types of nephritis, can be foretold with the same degree of assurance.

A long series of observations on the absolute and relative amounts of ammonia found in the urine in cases of nephritis are available. What has been lacking is their proper interpretation. Rudolph von Jaksch, finding the ammonia output high in a number of nephritics, declared the nephritides to represent a type of acid intoxication. It is a view with which I heartily concur in spite of the many criticisms of it that have appeared since von Jaksch's original communication.

XIII

PROPHYLACTIC MEASURES AGAINST NEPHRITIS. CARE OF THE SURGICAL AND MEDICAL PATIENT

It becomes apparent from what we have said above that *the mere diagnosis of nephritis has little meaning. It is as complete as a diagnosis of "dropsy," "fever" or "headache."* We found the nephritides to divide themselves into three groups—

into a toxic type in which a poison from some source affects the kidney, an infectious type again essentially toxic in nature but harboring organisms in the kidney itself, and a vascular type in which destructive lesions are consequent upon involvement of the blood vessels of the kidney by vascular disease. The first of these necessitates search for the source of the toxic agent; the second for the source and type of the infection in the kidney; the third for foci of infection responsible for the primary changes in the blood vessels. The infections of the kidney and vascular disease of the kidney come to us, at present, largely ready made, and so in these patients we must content ourselves with stopping, if possible, the progress of their pathological states and counteracting as well as we may their effects upon the kidney. We can do most from a prophylactic standpoint for the toxic nephritides. Evidently, if alkali, salt, carbohydrate and water relieve the signs and symptoms of the established toxic nephritis (and of the toxic portion that may be present in the other nephritides) the same measures will largely suppress or prevent their development if used prophylactically. It is more spectacular, by the use of alkali and salt to save a woman in convulsions, say from a pregnancy intoxication, but it is better medicine to instruct her in the methods of preventing such a condition altogether. And what is true of a pregnancy is true of any other established or anticipated type of intoxication in which disturbances from the side of the kidney are feared.

Our surgical and medical wards are filled with patients about to be operated upon or ill of various maladies in whom we can do much to lessen or shut out entirely such possibilities.

§ 1

An interesting and easily manageable group is furnished by the surgical patients. Much of their ante-operative preparation used to be and, in some places still is, of a type to guarantee from the outset a maximum of discomfort and even danger to the patient. Routine examination of the urine of patients about to be operated upon, even when not suffering from infections or intoxications likely to be complicated by nephritis, shows that in the days before their operations they are usually pushed into a state in which post-operative complications are very likely to

appear.[1] Commonly, the urine shows even before operation a high hydrogen ion acidity (acid to methyl red or even para-nitrophenol). Such patients make poor surgical risks, and should be given the benefit of preliminary treatment. The mental anxiety so common in the surgical case expresses itself physiologically by increased muscular tone, and this declares itself chemically by a great acid production which mirrors itself in the high acid findings in the urine. How much the intelligent reassurance of the surgeon must mean to such a patient is obvious.

Patients are also thoughtlessly ordered upon a "light diet." In this way the acid products of a starvation diet are added to those already present from other sources. Unless there are specific reasons against it, *a surgical patient should be fed to within a few hours (about six) of his operation,* and since carbohydrate starvation is the commonest and earliest form, special attention should be paid to getting an adequate sugar-starch ration into him in any form he may desire (potatoes, mush, toast, bread, sugar, candy).

In addition the patient should be fed alkali in some agreeable form. Any scheme for accomplishing this is good, but the use in large quantities of artificial or natural alkaline waters is perhaps simplest and best. If conveniently possible the alkali should be used for several days before the operation and *up to the point where the patient has a persistently neutral or somewhat alkaline urine.* A patient that goes upon the operating table with highly acid urine, or with a high ammonia coefficient, or shows qualitative disturbances in his metabolism as evidenced by acetone, diacetic and betaoxybutric acid in the urine, is in this proportion a bad surgical risk. An apparently poor risk, free from such findings, is almost certain to withstand anesthetic, the necessary trauma of operative interference, etc., without difficulty.

James J. Hogan, Hayward G. Thomas, Gordon F. McKim, Charles A. Pauson and William Mithoefer have long prepared their surgical patients in this manner, and find that they do better than on the old expectant scheme. The patients recover more rapidly from the effects of their anesthesia, they are without headache (absence of brain œdema) they vomit little or not at all

[1] For a report of fatalities due to "acidosis" in surgical patients see W. B. Russ: Jour. Am. Med. Assoc., **61**, 1618 (1913).

(absence of œdema of the medulla), they urinate an hour or two after the operation (absence of kidney œdema and early presence of "free" water), and the urine is practically free from the acetone, diacetic acid, albumin and casts so common post-anesthetically. Moreover, the traumatized tissues at the seat of the operation swell less and are less painful (less œdema).

McKim, for example, found that in a series of eighty surgical operations on the prostate, treated on the old expectant plan, he encountered much post-operative nausea, vomiting and gaseous distention of the bowel and some evidences of shock. Two patients became maniacal after the operations. Of a second series of fifty cases, in which nothing in operative technic or general hospital care was changed except that the patients were fed to within a few hours of operation and were given sodium bicarbonate and magnesium oxid, with much water until the urine was persistently neutral to litmus, he writes: "There has not been a single case of post-operative vomiting, practically no gas distention, and not one case of shock. The excellent condition of patients so handled is not to be compared with that of such not previously alkalinized. They are in better spirits mentally, in less pain and heal more quickly. This sounds strange, but my last cases have healed more quickly by a week."

The toxic effects of an anesthesia so far as the kidneys are concerned deserve consideration from several viewpoints. In the first place, no anesthetic, be this chloroform, ether or nitrous oxid, can produce its desired effects without interfering with the oxidation chemistry of the body. In fact, anesthesia depends largely, if not entirely, upon such an effect. We need not, however, add to this load by giving the patient too little oxygen. One of the superior merits of nitrous oxid-oxygen anesthesia resides in the fact that oxygen accompanies it. The other advantage is that profound anesthesia may be obtained quickly and be gotten over quickly—the nitrous oxid is, in other words, highly volatile. There is absent in consequence what might be termed the post-anesthetic or post-operative anesthesia of several hours' duration always incident to chloroform, ether and similar anesthetics.

It should also be remembered that the bad effects of an anesthesia are not simply a function of its length and the quantity of anesthetic used. Alvin Powell [1] found in a carefully studied

[1] Alvin Powell: Personal communication (1913).

series of operation cases that patients in whom but little anesthetic was used (and in whom perfect muscular relaxation was not obtained) showed more casts, albumin, etc., in the urine than those anesthetized longer and more deeply. On the other hand, very deep anesthesia was again followed by more albumin and casts. These facts are to be interpreted as follows: The bad toxic effects avoided by use of but little anesthetic are more than counterbalanced by those incident to the great acid production consequent upon imperfect muscular relaxation. The imperfectly anesthetized subject responds with muscular contraction to the irritation due to surgical trauma. Surgeons seem constantly to forget that even when such relatively "deep" reflexes are no longer apparent still deeper ones which happen not to show themselves in external movement are still being elicited. A medium degree of anesthesia increases the toxic factor of the anesthetic but eliminates the acid factor due to muscular rigidity. In deep sleep a maximum of interference with normal oxidation chemistry is again assured by the anesthetic itself.

Similar considerations hold in determining the value of morphin, atropin, scopolamin, and similarly acting drugs administered before or after an operation. In my own opinion atropin and scopolamin might well be eliminated. Atropin is valueless as a cardiac "stimulant" and is one of the worst of drugs in its ability to interfere with the normal oxidation chemistry of cells, while scopolamin acts as a cerebral excitant quite as often as a depressant. I have never, in surgical patients, seen atropin do good, while I am confident that it was responsible for several accidents (glaucoma, cardiac insufficiency, "shock," acute urinary suppression). Suprarenal derivatives should also be used carefully. While they guarantee a dry operating field, they as surely guarantee a bleeding field later. As E. C. VAN LEERSUM[1] has shown, in irreproachable experiments, the vasoconstrictor and blood-pressure-raising effects of epinephrin last only a few minutes to be followed by a vasodilatation and drop in blood pressure to far *below* the normal which lasts *days*. Morphin or morphin derivatives therefore remain alone to be considered. With a good anesthetist even their administration before an operation may be only a handicap. With a poor anesthetist, their bad effects may be offset by the

[1] E. C. VAN LEERSUM: Pflüger's Arch., **142**, 377 (1911).

assurance of better muscular relaxation and the elimination of acid production from this source.

The use of narcotics after operations becomes a matter of balancing their bad effects in interfering with the oxidation chemistry of the body against the good effects incident to elimination of the great muscular reaction, etc., consequent upon pain. The value of local anesthetic measures (cocain, novocain, etc.), as in nerve blocking and in tissue infiltrations, is similarly explained. Their use prevents pain impulses from reflexly expressing themselves in increased muscular tone, but it should be clearly borne in mind that their careless or immoderate use is not without bad effects.[1]

In the after-treatment of these surgical patients, a plentiful supply of air and an early reestablishment of a carbohydrate-rich diet with fruit juices, and alkaline drinks does much to hasten convalescence. The reasons for this are self-evident. Air not only means opportunity for the rapid elimination of the volatile anesthetics but the presence of much oxygen for the oxidation of lactic and other acids. As FLETCHER and HOPKINS have shown, a "fatigued" muscle—and the surgeon should remember that his worn out or mildly "shocked" surgical patient is suffering the same kind of chemical fatigue in all his voluntary and *involuntary* muscle—will oxidize a third of its content of lactic acid in a couple of hours and over half of it in six or seven. The patient recovering from an anesthetic needs food. His nausea—which is not likely to be present if properly treated beforehand—is of central origin, not peripheral. Withholding food from the stomach will not cure it while such starvation may actually make the central disturbance worse. To control the psychic factor in gastric secretion and motion the patient should be asked what he *desires* and then should be led to desire carbohydrates, as the ices, ice creams, fruit juices with much milk sugar, creamed toasts, milk with milk sugar, etc. The so necessary alkali may be given by mouth or rectum but

[1] I cannot help but endorse here the excellent surgical methods urged by GEORGE W. CRILE in the protection of his patients against shock, and this in spite of the fact that I am not of a mind with him regarding its nature and cause. I cannot escape the conviction that the central nervous system changes which he describes (swelling of cells with changes in their staining properties) are not the causes but the consequences of shock and to be explained in the same way as the œdemas which characterize the swollen glandular and body tissues elsewhere in the organism. I shall return to this question in detail at another time.

enough must be administered—enough to keep the urine constantly neutral to litmus or alkaline to methyl red. Carbonated alkaline drinks may be used or baking soda enemas, three to four times in the first twenty-four hours and then twice daily—but always in sufficient numbers to accomplish neutralization. It is too often forgotten how much acid production follows the ordinary anesthetic. Maurice Nicloux and G. Fourquier[1] calculate that 50 per cent of the administered chloroform is broken into acid compounds and that for each gram thus broken a gram of sodium (or more of potassium) is needed to accomplish neutralization. When other anesthetics are used the same acid poisoning follows, the degree being determined by the amount and nature of the anesthetic used. As Evarts Graham[2] has found, the poisonous effects of the anesthetics largely parallel the amounts of hydrochloric acid which they yield on breakdown which explains why tetrachlormethane, chloroform, dichlormethane, ether and chloral hydrate are decreasingly poisonous in the order named.

In much the same way that we have discussed the protection of a patient against the effects of an anesthesia intoxication we may also guard him against the consequences of other intoxications. The effects of arsenic (salvarsan) offer a case in point. It may be only good fortune, but I think not, that I have never had a serious salvarsan complication and that none has occurred in the practice of my colleagues who before injection take the precaution of thoroughly alkalinizing their patients. The blindness (optic nerve œdema), headache (brain œdema), vomiting (medullary œdema), generalized œdema, decrease in urinary output with blood, casts and albumin (œdema of kidneys), pain in various sensory nerves, etc., which have been so frequently described, and which, when sufficiently severe, may end in death, are more easily interpreted as œdemas due to arsenic intoxication than as syphilitic manifestations fanned to fire by the arsenic injections. In consequence of syphilitic disease, tissues on the verge of œdema through connective tissue overgrowth, defective blood supply, pressure, etc., are pushed over the line by the arsenic intoxication. Thorough alkalinization beforehand (and treatment with potassium iodid has much the

[1] Maurice Nicloux and G. Fourquier: Presse Médicale, **20**, 729 (1912).
[2] Evarts Graham: Jour. Exp. Med., **22**, 48 (1915); Jour. Am. Med. Assoc., **69**, 1666 (1917).

same effect) tends to prevent the disastrous consequences of such superimposed œdema. And let me add that I have used the salvarsan in the very cases in which it is ordinarily forbidden, namely in tabes, optic nerve and brain lesions, arteriosclerosis, aneurysm and kidney disease (so-called chronic interstitial, nephritis with high blood pressure) when I felt syphilis was a factor in the case.

§ 2

What has been said of surgical patients holds with equal force for many of the medical ones. Their routine examination reveals a great majority suffering from medium and at times high-grade states of acid intoxication. Analysis of the urine is our best guide to the discovery of such handicapped individuals, but the retention of water by the patient (as evidenced by weighing him), the slight general œdemas so frequently observed, the headache, the vomiting, the rapid pulse, the quickened respiration [1] and the appearance of albumin and casts in the urine all further betray the fact. The tests for low alveolar carbon dioxid tension and the measurements of the "alkali reserve" in the blood which have become popular during the past years are all expressive of the same fundamental acid intoxication. The amount of carbon dioxid in the expired air falls whenever any stronger acid appears in the blood and "blows off" the carbonic acid; while the "alkali reserve" must evidently fall whenever a draft has been made upon it by acid.

The sources for the acid production are, of course, many. The various intoxications incident to the infections lead to great acid production. To this are often added the acid effects of inadequate feeding. The food may be badly chosen or be insufficient in amount, or in his illness the patient may not take enough. If he becomes mentally excited or develops a convulsion, say in the

[1] The patient suffering from an acid intoxication from any source whatsoever cannot hold his breath as long as can a normal person. YANDELL HENDERSON (Jour. Am. Med. Assoc., **63**, 318 (1914)) with his customary keenness has indicated how this fact may be used as a simple and accurate guide to the degree of acid intoxication *clinically*. A normal person after resting for five minutes and then ordered to take a full but not abnormally deep inspiration can hold this with closed mouth and nose for 30 to 40 seconds. If partially poisoned with acids the breath cannot be held so long, a patient able to hold it only 20 seconds or less constituting a bad surgical prospect.

course of an infectious disease, then the products of such excessive muscular work are added, and his precarious state is further augmented.

It must be self-evident how much we can do both to prevent and to relieve these conditions. It is not difficult in beginning cases to feed enough alkali by mouth to keep the urine persistently neutral. If such proves inadequate, enemas of sodium bicarbonate (12 to 18 grams to the liter) or of sodium carbonate and salt may be used. The necessity of sufficient carbohydrate feeding has long been emphasized by different authors. When the oral route is not adequate, rectal injections of dextrose (glucose) do much good. But it should be remembered that only dextrose is easily absorbed, and that the common practice of giving starch, milk, milk-sugar or cane sugar enemas and like concoctions is valueless, for these higher carbohydrates are scarcely absorbed. Moreover, *several hundred* (about 500) grams of carbohydrate are required per day—a fact which will suffice to emphasize the complete inadequacy of the teaspoonful methods of feeding so commonly encountered in practice.

When both mouth and rectum are inadequate, good, and at times, startlingly good results are obtained by giving chemically pure dextrose *intravenously*. For reasons previously emphasized, this is best given very slowly in concentrated form (45 grams dextrose per 100 cc. of water).

To the mind which never asks what is the nature of the processes that characterize disease and what is the purpose and the ultimately accomplishable in therapy, the attempts at analysis, and the suggestions for treatment outlined in these pages, can mean but little. What I have said has been variously commented upon. To Theodore C. Janeway my reports on the relief of patients, in whom objectively judging colleagues had felt only a fatal issue possible, "read like the cures of the nostrum venders."[1] To others the patients would have recovered anyway. Some believe the whole procedure valueless. Henderson, Palmer and Newburgh find it "harmful and productive of human suffering."[2] How proper use of alkali,

[1] Theodore C. Janeway: Unsigned review of first edition of my "Nephritis." Arch. Int. Med., **9**, 637 (1912).

[2] Henderson, Palmer and Newburgh: Jour. Pharm. and Exp. Therap., **5**, 466 (1914). The opinion is shared by Lawrence Litchfield: Jour.

salt and sugar can produce such strange results is incomprehensible. Some hold what I have written as essentially true.[1] In the dilemma I advise anew that the objective thinker in medicine reject my views and first treat his patient with nephritis and its alleged consequences by more approved methods. If he should feel that his patient is going to die, alkali, salt and sugar might be tried. If the patient dies, the expected will merely have happened. If he lives, it proves nothing, but it may encourage repetition of the experiment. And this, I feel, is all that is necessary.

Am. Med. Assoc., **63**, 307 (1914). The value of LITCHFIELD's evidence has been analyzed by PAUL G. WOOLLEY: Jour. Am. Med. Assoc., **63**, 596 (1914). Similar criticism by A. R. MOORE: Univ. Calif. Pub. Physiol., **4**, 111 (1912); Pflüger's Arch., **147**, 28 (1912); ibid., **148**, 167 (1912); Jour. Am. Med. Assoc., **59**, 423 (1912) and **60**, 345 (1913), I have answered myself. FISCHER: Jour. Am. Med. Assoc., **59**, 1429 (1912); **60**, 348 (1913).

[3] E. O. SMITH: Lancet-Clinic, **107**, 213 (1912); ARTHUR D. DUNN: Lancet-Clinic, **108**, 8 (1912); ALBERT J. BELL: Am. Jour. Med. Sci., **144**, 669 (1912); personal communication (1914); MAGNUS A. TATE: Bull. Acad. Med. Cincinnati, **1**, No. 22 (1912); Lancet-Clinic (1912); EDGAR G. BALLENGER and OMAR F. ELDER: Jour. Am. Med. Assoc., **62**, 197 (1914); RUFUS SOUTHWORTH: Lancet-Clinic, Sept. 5 (1914); GORDON F. MCKIM, Personal communication (1914); H. LOWENBURG: Jour. Am. Med. Assoc., **63**, 1906 (1914); JAMES J. HOGAN: California State Jour. Med., **13**, 50 (1915); Lancet-Clinic, **113**, 6 (1915); Jour. Am. Med. Assoc., **67**, 1826 (1916); GEORGE J. GRINNAN: Virginia Med. Semi-Month., **20**, 523 (1916); H. B. WEISS: Jour. Am. Med. Assoc., **68**, 1618 (1917); Ohio State Med. Jour., **13**, 595 (1917); J. MICHELL CLARKE: Brit. Med. Jour., **2**, 239 (1917); HERBERT BROWN: Personal communication from Flanders, received Sept. 1, 1917; W. DE B. MAC NIDER; Jour. Exp. Med., **23**, 171 (1916); ibid., **26**, 19 (1917).

PART SEVEN

GLAUCOMA

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I

ON THE NATURE AND CAUSE OF GLAUCOMA

From a pathological standpoint, glaucoma represents simply one of the local œdemas. From a clinical point of view, all its signs and symptoms have since von Graefe's teachings (1860) been correctly referred to the increased intraocular pressure induced through the abnormally large amount of water held by the eye. How does it come to do this?

A glance at any of the standard works on ophthalmology [1] shows no dearth of attempts to answer the question, but experiments planned to support the views advanced by the various authors have been singularly unsuccessful. For the most part, when not simply referred to the occult properties of "living" matter, these explanations are identical with those given for œdema anywhere else in the body. They are familiarly mechanical in character in that an increased lymphatic or blood pressure is supposed to *force* an abnormally large amount of liquid into the tissues of the eye. Such increased pressures are generally held to be induced through interference with the outflow of lymph or of blood from the eye occasioned through obliteration of the "filtration angle," etc.

The experiments detailed in a previous section of this volume,[2] and instituted in order to ground experimentally the colloid-

[1] See, for example, Ernst Fuchs: Augenheilkunde, Zwölfte Auflage, 523; Leipzig u. Wien (1910); Priestly Smith: Glaucoma, London (1891).

[2] See page 169.

chemical conception of œdema, showed clearly that *the most intense grades of glaucoma can be induced experimentally in an eye in the entire absence of any circulation.* This fact coupled with the well-known observation that any experimental increase in the pressure of the liquids circulating through an eye is not followed by glaucoma arraigns all the explanations thereof which look to an increased pressure as in itself of essential importance in its causation. Such considerations compel the conclusion that the cause of glaucoma resides in the tissues of the eye itself, and that it becomes glaucomatous not because fluid is pushed into it, but because through changes in it, it *absorbs* an increased amount. That the amount of such absorption is sufficient to explain the severest grades of glaucoma is clearly evidenced by the fact that through the mere presence of a little acid, a beef eye can be made to absorb enough water to rupture its enormously thick sclera. This is a grade of glaucoma that exceeds anything ever seen clinically. Our experiments further show that *this increased absorption of water is dependent upon the colloids in the eye, for not only is it built up of a series of different colloids* (*sclera, cornea, lens, vitreous humor*), *but the same conditions which govern the absorption of water by protein colloids also govern the absorption of water by the eye.* On the ground of these experiments *we can, therefore, no longer insist that an eye becomes glaucomatous because water is forced into it. It does this because chemical changes occur within it which increase the capacity of the ocular colloids for holding water so that these are enabled to absorb water from any available source.* In our experiments with enucleated eyes this source is the solution into which the eye has been dropped; in the body it is the liquids flowing about or through the eye.

The chemical changes in the eye which clinically lead to glaucoma are the same as those which may give rise to an œdema anywhere else in the body. In a large number of cases, circulatory disturbances in the eye are unquestionably present which permit of an accumulation of carbonic acid and of such other acids as are a constant accompaniment of states of oxygen want. In the glaucomas due to infections or, in general, to the toxic agents capable of producing "degenerative" or inflammatory changes (in the strict pathological sense of the term) in the eye we have to look to the chemical alterations thus induced for the cause of the altered hydration capacity of the ocular colloids. Many

of these intoxications lead to an altered oxidation chemistry in the affected tissues and an accumulation of acids; but the direct action of chemical substances (like urea or certain amins), which in their ability to increase the hydration capacity of protein colloids act like acids, must also be kept in mind. Under the influence of proteolytic ferments, proteins having a low hydration capacity can also be converted into such as have a higher one. Ordinary gelatin can thus be converted into Beta-gelatin. WOLFGANG OSTWALD'S studies show Beta-gelatin to be capable of greater swelling than the unchanged. It is therefore conceivable that in inflammation (whether in the eye or elsewhere) an increased hydration capacity of the involved tissues may result from "autolytic" changes occurring in them even when no abnormal storage or production of acids in the part occurs. Perhaps the best evidence of the correctness of this colloid-chemical conception of glaucoma is furnished by the following clinical observations.

II

ON THE RELIEF OF GLAUCOMA

1. Local Measures

The experiments on the swelling of enucleated eyes familiarized us not only with ways and means by which an intense glaucoma can be induced in an eye, but showed how *the development of such can be prevented, or, once established, be made to go down again.* While under ordinary circumstances little is gained by simply reducing an œdema, there exist a number of clinical forms of it which are in themselves dangerous. Glaucoma is one of these, which through its existence for even a short time may permanently blind an eye. To be able to combat the œdema in such a case is, therefore, not a useless procedure.

In the experiments on the swelling of eyes we learned that the presence of any salt markedly decreases the amount of water that an eye will absorb in an acid solution. The question therefore arose whether the instillation of salt solutions into the eye might not be followed by relief in clinical cases of glaucoma.

Hayward G. Thomas and I decided to test the matter.[1] The instillation of salt solutions was not, however, to be entered upon hastily, for experiment had shown that *while all salts reduce the amount that an eye will swell in an acid solution, a large number also increase its tendency to develop corneal opacities.* There would be little gained, except so far as relief from certain subjective symptoms might be concerned, by guarding an eye from blindness through glaucoma while blinding it through the agency employed for its relief. *There exist, however, a number of salts which inhibit markedly the swelling of eyes in acid solution and at the same time not only do not increase, but even decrease the tendency to the development of these corneal opacities.* In other words, the use of these salts tends to prevent the development of even that well-known turbindess of the cornea which is so constant a sign in clinical cases of glaucoma, and which one never fails to get in the experiments on eyes that I have described.[2] These salts are the citrate, tartrate, sulphate and phosphate of sodium and potassium.

After a number of preliminary tests sodium citrate was chosen as the salt best suited for clinical use. Only the chemically pure salt should be used, in concentrations varying from m/8 to m/6 solution. Expressed in percentage the former is equivalent to a 4.05 per cent solution, the latter to a 5.41 per cent solution of the ordinary crystallized sodium citrate. The m/8 solution has an "osmotic" pressure below that of the human tissue fluids, the m/6 one slightly above. The injections are made with a fine-needled hypodermic under the conjunctiva in the usual manner adopted by ophthalmologists, and are preferably preceded by the use of cocain and adrenalin solutions. Enough of the sodium citrate is injected to distend gently the connective-tissue spaces (5 to 15 drops). Immediately following the injection the patient suffers some pain. While this is usually insignificant, it is fairly severe in certain cases. Alternate hot and cold compresses laid over the eye may help to ease it. In any event it disappears in a few minutes. In the severer cases of glaucoma

[1] Hayward G. Thomas and Martin H. Fischer: Annals of Ophthalmology, **19,** 40 (1910); Hayward G. Thomas: Journal of Ophthalmology and Oto-Laryngology, **5,** 205 (1911).

[2] See the succeeding page 806.

we use the stronger sodium citrate solution, in the milder ones or for subsequent treatment the m/8 is sufficient. This will, in fact, rapidly reduce the tension in even the severe cases of glaucoma. Later in the treatment a mixture of one part of the m/8 sodium citrate solution, with two to four parts of a "physiological" (0.9 per cent) sodium chlorid solution, is sufficient. It need hardly be emphasized that such citrate solutions must be sterile and that since bacteria readily decompose them, they need constantly to be freshly prepared. Our results may be summed up as follows:

Subconjunctival injections of m/8 *to* m/6 (4.05 *to* 5.41 *per cent*) *solutions of the crystallized, chemically pure sodium citrate in clinical cases of glaucoma are harmless and always followed by a prompt fall in ocular tension. The fall may be appreciable within ten minutes after the injection and ultimately so great as to make the eye have a subnormal tension. The effect of such injections lasts from three to six days (or even more) and is accompanied by a relief of all the subjective symptoms of glaucoma* (except, of course, any blindness due to permanent structural changes).

2. Systemic Measures

As the ophthalmologists have long recognized, many factors lying outside of the eye play a rôle in the development of the glaucomatous attack. The problem is, as a matter of fact, analogous to the acute œdemas that may develop in any of the other organs of the body, as in the brain (uremia), the kidney (nephritis), the optic nerve (papillo-œdema), or the liver (cloudy swelling, liver necrosis). And as in such œdemas we err when we observe only the specifically involved tissues, so also in glaucoma.

It is self-apparent that a hydrating agency such as an accumulation of acid in an eye leads to a swelling of the ocular colloids, no matter whether its origin is purely local (say the consequence of an arterio-sclerosis of the blood vessels of the eyeball), or whether to this local acid production is added the effect of acid produced elsewhere in the body and carried into the eye through the circulation.

The conditions that lead to an abnormal production or accumulation of acid in the body as a whole are many, and

constitute a list that is familiar to every ophthalmologist under the heading of etiological factors concerned in the production of glaucoma. Starvation, an excessive protein diet, hard muscular and mental work, excessive consumption of sour wines, various intoxications (anesthetics, alcohol, arsenic), the infections, the severe anemias, generalized arterio-sclerosis, uncompensated heart lesions, exposure to cold, are all associated with an abnormal production or accumulation of acid in the body. Any of these may be the deciding factor that pushes an eye on the verge of glaucoma from a local condition, over the line, and so precipitates the glaucomatous attack.

Local treatment alone, be this a subconjunctival injection of sodium citrate or one of the more popular iridectomies, sclerotomies, or trephinings, does not affect the contributions which are being made by the extraocular factors. To meet the situation we must treat the whole man.

To begin with, it is clearly indicated, therefore, that we remove as many as possible of these extraocular conditions. But we are likely to find that some of them cannot be removed, or at least not with sufficient speed to make it count in our patient who finds himself in the midst of a glaucomatous attack. Under these circumstances we have only one other door open to us, and that is to combat their consequences. In practical terms this again means a neutralization of the abnormal acid content by giving alkali; the administration of salts to reduce the swelling of all the colloids in the body including those of the eye; and an administration of carbohydrate if indicated.

How in actual practice this is accomplished may be illustrated by the following history of a case of glaucoma which Hayward G. Thomas invited me to see.

Case XXVIII.—Mr. F. C., aged seventy-two, goes to his office daily. He has for fifteen years had some albumin and casts in his urine. Unless his carbohydrates are consumed in moderation, he also has sugar. All his superficial arteries are easily palpable and tortuous, and his heart is hypertrophied. The second heart sound is accentuated. His blood pressure is constantly 190, and rises to 210 mm. of mercury. He has never had a generalized œdema.

On July 16, after a day of mental and physical fatigue, he developed pain in his left eye and left temple, noticed that his eye was "bloodshot," and that he could not see the outline of objects clearly. The condition continued through the night, the pain being so severe as to keep him

awake. In the morning of July 17 his state had not improved, and his eyesight had fallen off still more. He tolerated his condition throughout this day, and through the succeeding night and day, by which time he declared himself completely blind in the affected eye.

In the middle of the afternoon of July 18 he summoned Dr. THOMAS, who found the eye hard (tension +3), pupil dilated to size 5, MORTON scale, conjunctiva very much chemosed, cornea slightly steamy—a typical attack of the so-called "acute inflammatory glaucoma." Instillations of eserin were at once begun, and the patient moved to the hospital. The instillations were entirely without effect.

At 9 P.M. a slow injection of the following solution into the rectum was started:

Sodium carbonate (monohydrated, $Na_2CO_3 \cdot H_2O$)..	4.3 grams
Sodium chlorid.....	14.0 grams
Distilled water, enough to make.....	1000 cc.

The patient retained the solution well, and by midnight had taken up the whole liter. The tension in the eye had fallen appreciably an hour after the injection was started, and at midnight was normal to the touch. At the same time the subjective symptoms of the patient improved, and he went to sleep. At 4 A.M., 500 cc. more of the above formula were injected and retained. At daybreak the patient was able to recognize gross objects, and through the day his vision became steadily clearer. He remained under observation in the hospital for two days longer. No new symptoms developed, and he was discharged with completely restored vision.

In interpretation of the clinical history just detailed, which is characteristic of the larger number of glaucomas encountered in patients beyond forty, I would say that vascular disease was primarily responsible for a diminished oxygen supply to the eye. For years such a change had led to no appreciable symptoms so far as the eye was concerned, but one day in consequence of unusual muscular and mental fatigue, aided possibly by an "acidosis" incident to his sugar intolerance, the acid accumulation from these sources added to that initially incident to the bad blood supply to the eye, sufficed to increase so materially the hydration capacity of his ocular colloids that they swelled to the point of giving him easily recognized signs and symptoms—a frank œdema of the eyeball, a glaucomatous attack. But the reduction of this attack did not change his blood vessel disease, and so it could safely be predicted that in consequence of another period of hard work or dietary indiscretions he would again get eye symptoms.

As a matter of fact, Dr. Thomas reports that after two months of freedom from symptoms the patient tired of his restricted activities and his alkalinized diet and had two more attacks of increased tension, though not of a severe type. The first of these was controlled by the same eserin solution which in the initial severe attack had been unable to reduce the tension. In the second of these milder attacks the eserin again proved unavailing, even though a contraction of the pupil resulted. An active administration by mouth of alkali and table salt with calomel and magnesium citrate was turned to, and while using these the tension returned to normal.

When we have succeeded in relieving the frank glaucomatous attack in which we are likely first to see our patient it becomes our purpose to prevent further attacks. To do this we make use of the principles already enunciated, though it is not necessary, of course, to work so aggressively. We need again to recognize and avoid as far as possible those conditions which directly or indirectly threaten to increase the hydration capacity of the ocular colloids and to increase the margin of safety against such. This means a sane restriction of the physical and mental activities, a careful control of the water intake and a quieter insistence on a diet rich in alkalies and salts.

III

SOME COMMENTS

Prompt as may be the relief of tension with its associated symptoms in glaucoma after subconjunctival sodium citrate injections or the use of alkaline hypertonic salt solutions by rectum, it must be clearly understood that neither of these constitute a "cure" for it. As a cure of glaucoma we could only consider a removal of the condition or conditions which are responsible for the development of the substances which increase the hydration capacity of the ocular colloids. If these are acids, the product of a circulatory disturbance or of an infection, then clearly the real cure resides in a correction of the circulation to the eye, or in the removal of the infection. But even toward such ends do these dehydrating methods help. In the progressive development of a glaucoma the swelling of the col-

loids tends to compress the blood vessels passing into and out of the eyeball. The natural tendency of a glaucoma is, therefore, to make itself worse. Writers on ophthalmology are in the habit of laying great stress on the obliteration of the filtration angle. *Obliteration of the filtration angle is frequently said to be the cause of glaucoma. It is a consequence,* as evidenced by the fact that enucleated eyes rendered artificially glaucomatous by being placed in acid solutions show the same progressive decrease in the depth of the anterior chamber that is noted in clinical cases. The matter is easily explained through the unequal swelling of the different colloids of the eye, those posterior to the lens (sclera, choroid, vitreous) being capable of greater swelling than those anterior to it (cornea, aqueous).

Through this unevenness in swelling the cilary body is crowded against the sclera—a process in which the blood vessels of the ciliary body become pinched. The resulting embarrassment in the circulation (with its lack of oxygen, accumulation of carbonic and other acids, etc.) is then added to whatever conditions are already active in producing the glaucoma. To reduce the swelling of the ocular colloids, even though but temporarily, is, therefore, to improve the circulation through the eye and in this way to contribute not inconsiderably toward the restitution of normal conditions within it. If the glaucoma is the consequence of some acute accident then its prompt relief may not only save the eye from blindness through pressure, but by helping toward the re-establishment of a normal circulation through the eye furnish the necessary conditions required for the repair of any pathological process.

The principles underlying both the local therapy of glaucoma (subconjunctival injections of sodium citrate) and the general therapy, as touched on here, are of course the same, and so the fact will not prove strange that both produce a lowering of tension. I now urge and rely chiefly on the withdrawal of all water intake by mouth and the use of the rectal injections of hypertonic alkaline solutions (either the sodium carbonate-sodium chlorid solutions or the strong sodium bicarbonate solution recommended above) while teaspoonful doses of saturated magnesium sulphate solutions are given by mouth at hourly intervals for four to eight doses. This regimen is followed not alone because glaucoma is so often but a local expression of a general state, but

because, while various observers [1] have reported uniformly favorable results from the use of sub-conjunctival injections of sodium citrate, others have objected to them, and some have even maintained that their use increased the tension.[2] While I have myself never observed such a result, the proper use of alkali and salt by mouth and rectum produces so effective a dehydration of the body (including the eye) that I have in the past seven years made it a rule to try first this simpler method for two or three hours before turning to subconjunctival injections. But whatever scheme is used let me here again insist that the various mixtures of alkali and salt, and sugar and water which I have suggested and to which my name is often linked have not in themselves any special virtue. Virtue resides in working out a really effective scheme for dehydrating swollen colloids, and the attending physician or surgeon is at liberty to accomplish this by any means which he thinks best. [3]

Some of my critics have utilized their failure to obtain a fall in tension after subconjuctival sodium citrate injections to combat the colloid-chemical theory of glaucoma. Without charging them with improper preparation or improper use of their solutions—I find men constantly modifying the concentration or the amount of the injection to suit themselves—it might be well to inquire why they failed.

When a solution of sodium citrate is injected subconjunctivally, we desire to have the sodium citrate diffuse into the eye and so decrease the hydration capacity of the ocular colloids (shrink them). We use water along with the salt only of necessity. But if the glaucoma is of a severe type it means that the hydration capacity of the ocular colloids is exceedingly high. It may happen in consequence that when we inject an aqueous solution subconjunctivally the water is absorbed before the salt gets in, in which case the swelling would actually be further augmented. The bad result is not due to the sodium citrate, but to the inability to get the salt into the eye in sufficient concentration. Or, if extraocular factors are playing a good part in the produc-

[1] See for example VAN DER HOEVE: Klin. Monatsbl. f. Augenheilk. N. F., **13**, 602 (1912).

[2] See GILBERT: von Graefe's Arch. f. Ophth., **32**, 438 (1912).

[3] Decrease in intraocular tension has been accomplished by R. T. WOODYATT, W. D. SANSUM, and R. M. WILDER (Jour. Am. Med. Assoc., **65**, 2067 (1915); ibid., **68**, 1885 (1917)) by injecting intraveneously strong dextrose solutions.

tion of the glaucoma as is the case when there is a generalized acid accumulation resulting from a weakened heart, overwork, starvation, etc., this cannot, of course, be neutralized by the instillation of a few drops of some salt solution under the conjunctiva.

Others of my critics have objected to the lack of tonometric readings in my reports. A desire always to substitute actual figures for the results of human judgment together with the easy availability of the SCHIÖTZ tonometer certainly tempts one to fill out this gap, and yet I have hesitated in this direction, and for the following reasons. First, the reduction of tension in an eye must be of so marked a character if it is to serve as the basis for a suggested therapy that it must be readily discernible even to the, perhaps, but slightly practiced touch of any physician. I would think little of a suggested therapy for glaucoma which reduced tension so slightly that only a tonometer could recognize the change. Second, tonometric measurements cannot be made without instillations of cocain, holocain or similar substances into the eye, and manipulations of the eyeball which are not without effect. Such instillations and manipulations themselves lead to an increased œdema, and so tend to maintain or augment whatever increased tension already exists in the eye.

There is evidence of a marked tendency in the recent literature on the treatment of glaucoma to urge more strongly than formerly the use of myotics and constitutional remedies for the relief of glaucoma. This has largely grown out of the fact that iridectomy all too often fails to give more than temporary relief. The problem is really the same as that encountered in brain œdema, in nephritis, etc., which represent in the involved organs processes which if they affect the eye are called glaucoma.

A decompression operation, a stripping of the capsule, etc., may bring clinical relief (by permitting a better circulation through the swollen parts), as do sclerotomy, trephining, and similar surgical procedures when applied to the eye. But statistics on the after effects of operations in glaucoma are no better than those following surgical interference in brain œdema, nephritis, etc. The reasons for these failures, as well as the explanation of the occasional brilliant result, are, of course, not far to seek.

Behind an œdema of the eye lie the same possibilities which produce an œdema anywhere else in the body. Rarely are

such confined to the eye alone. And the effects and relative merits of a surgical operation, or a myotic, or sodium citrate, or alkali and salt by rectum can be foretold here as well as when a capsule stripping, a vasodilator, a diuretic salt or alkali are used in a brain œdema or a nephritis. When the swelling of the eye is due to a temporarily acting poison all may yield brilliant and permanent results, for when the tension has once been reduced the eye is saved, for the causes leading to the œdema have then also gone. *But when blood vessel disease—by far the commonest cause in our older patients*[1]*—is responsible for the increased tension,* it may again be reduced, but since this does not abolish the blood vessel disease, the tension is again liable to increase even if an iridectomy or a trephining has been done or alkali and salt have been properly used.

Many ophthalmologists know now and all will shortly learn that a diagnosis of glaucoma is as complete as a diagnosis of "dropsy," and as modern medicine is not content with the latter it will not long remain so with the former.

Glaucoma, except when it follows trauma or direct infection, is not a local disease but nearly always a local expression of systemic derangement. It will be blotted off the pages of ophthalmic literature not by more surgery but by a prophylaxis and therapy which recognizes and treats vascular disease, infection and intoxication involving the eye.

IV

ON THE NATURE OF CORNEAL OPACITIES

In clinical cases of glaucoma there is noted as one of its most constant signs more or less opacity of the cornea. In an entirely similar manner the cornea loses its transparency in the experimentally induced glaucomas already described. Since the essential change in the eye in glaucoma consists of an abnormal increase in the amount of water held by it, the view generally advanced by ophthalmologists that the observed opacities are

[1] In 22 patients with glaucoma 19 showed high blood pressure and other frank signs of vascular disease. The remaining 3 were younger individuals who had suffered from "rheumatism," with metastatic, infectious involvement of the eyes themselves. The eyes of one of these had been operated upon 13 times without benefit.

due to the absorption of water by the cornea does not surprise us. Such an origin for the opacities observed here has been extended to include those found in the other transparent media of the eye. Especially has the lens been believed to owe its loss of transparency in many conditions to an imbibition of water.

Serious objections seem never to have been raised against such a view, and this in spite of the fact that clinical cases of absolute opacity of the cornea or the lens may exist without any evidence of an increased absorption of water, while, on the other hand, even severe cases of glaucoma may come and go without more than a mere haziness of the cornea.

These paragraphs confine themselves to the question of the origin of *corneal* opacities, simply because these have been studied with greatest care. It seems, however, that what is here said regarding the cornea holds also for the lens [1] and the other transparent media of the eye. The opacities referred to, it need hardly be said, include only such as are the consequence of chemical disturbances in the eye, and have nothing to do with such as are the result of leucocytic deposits, connective tissue scars, etc.

Neither the presence of an increased or a decreased amount of fluid in the cornea is responsible for the appearance of an opacity. Such is produced whenever some of the colloid constituents of the cornea are precipitated, and depending upon whether the precipitation is only slight or very great, these opacities vary from being barely visible (steaminess of the cornea) to such as are intensely white (leukoma).

The effect of different solutions on the transparency of the cornea was judged in two ways, first in regard to the *rate* at which they permitted the development of an opacity, and second, in regard to the *intensity* of the opacity. The outer limits of the former vary from a few minutes to several days, for the latter from a turbidness scarcely visible to the naked eye to a whiteness like that of boiled albumin. The italicized conclusion is based upon the following facts.[2]

[1] For experimental details which may all be explained in the terms of colloid-chemistry on opacities of the lens and water absorption by it, see Phil. Botazzi and N. Scalinci: Arch. ital. Biol., **51**, 96 (1908); Rend. della Accad. dei Lincei, **27**, 305, 445, and 566 (1908); ibid., **28**, 225, 326, and 379 (1909).

[2] See Martin H. Fischer: Pflüger's Arch., **127**, 46 (1909).

(*a*) If an eye is simply allowed to dry, no opacity of the cornea develops. Mere loss of water, therefore, does not lead to its appearance.

(*b*) If an eye is laid in distilled water it gains in weight. In this process of water absorption the cornea takes a prominent part, yet no turbidness of this structure develops until quite late. Simple absorption of water, therefore, does not lead to an opacity.

(*c*) The presence of any acid favors the development of an opacity, but the different acids are unequally powerful in this regard. Nitric acid induces a corneal opacity more quickly than an equinormal oxalic acid, and this more quickly than an equinormal hydrochloric acid. Still less powerful are sulphuric and acetic acids in the order named. Clearly, therefore, the order in which acids induce corneal opacities is entirely different from the order in which they make eyes swell.

(*d*) We note a further discrepancy between the amount of water absorbed by an eye and the rate of development, or better, the intensity of a corneal opacity as soon as the effects of adding equimolar salt solutions of different kinds to any acid solution are compared. While every salt reduces the amount of water absorbed by an eye in an acid solution, some salts favor the development of an opacity while others distinctly inhibit it. The citrate, acetate, and sulphate, for example, inhibit the development of a corneal opacity, while the sulphocyanate, nitrate, bromid, and chlorid favor it.

(*e*) The effect of any salt seems to be made up of the algebraic sum of its constituent radicals. When a series of salts having a common base are compared, the order of the acid radicals is always the same, and when a series of salts having a common acid are compared, the order of the basic radicals is always the same. These orders are indicated in the two following lists, in each of which the radical most effective in producing an opacity is given first, that most effective in inhibiting it last.

Sulphocyanate, nitrate, bromid, chlorid, sulphate, acetate, citrate.

Iron (ferric), copper (cupric), calcium, strontium, barium, magnesium, ammonium, sodium, lithium (?).

The order in which different salts or, as we had best say, their constituent radicals, affect the production of corneal

opacities, is, therefore, an entirely different one from the order in which they influence the amount of water absorbed by the eye as a whole. The disproportion is illustrated in Fig. 217.

In *a* is shown the thickness of the cornea of an eye which has lain in distilled water for thirty-six hours and is still perfectly clear; in *b* that of an eye which has remained for the same length of time in n/110 hydrochloric acid. This eye burst six hours after being placed in the solution. The cornea is very thick, but only slightly opaque (ground-glass appearance). *c* was left for thirty-six hours in a similarly concentrated hydrochloric acid solution, containing magnesium nitrate in addition (20 cc. n/10 HCl+200 cc. m/3 $Mg(NO_3)_2$). Even though the

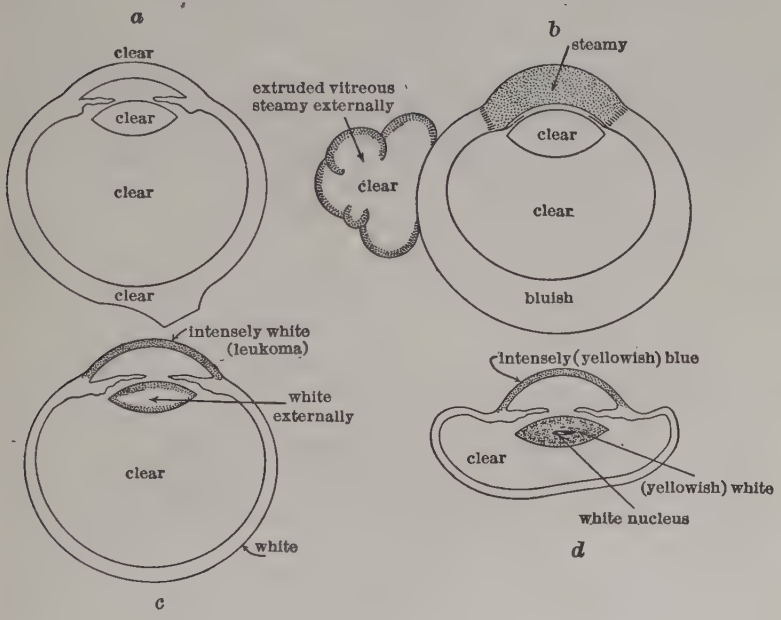

FIGURE 217.

cornea is not swelled—it is even thinner than normal—it has the intensely white color of boiled albumin. About the same condition of affairs is shown in *d*, which indicates the appearance of an eye thirty-six hours after being placed in n/110 hydrochloric acid solution plus ferric chlorid (20 cc. n/10 HCl+200

cc. m/3 ferric chlorid). In spite of the great loss of water, the thin cornea is intensely white (and stained slightly yellow from the iron chlorid).

(*f*) In the experiments on the swelling of eyes it was found that non-electrolytes in low concentration do not markedly affect the swelling of eyes in an acid solution. Nevertheless, most non-electrolytes appreciably inhibit the development of corneal opacities.

(*g*) All the above facts show clearly that *no* parallelism exists between the total amount of water absorbed by the cornea and the intensity or rapidity of the development of an opacity in it. The facts outlined are easily harmonized as follows: *While the eye as a whole swells, due to an increased hydration capacity induced in some of its colloids, a second colloid (of the type of casein) is being precipitated (dehydrated). A swollen eyeball with opacities in its clear media (glaucoma) is the analog of what in other organs is known as "cloudy swelling,"* [1] *and the conditions which bring it about are exactly the same in both.*

V

CLOSING REMARKS

This volume must not be ended without the request that should its contents tempt any clinician to try the therapeutic methods here advocated, it tempt him also to study the considerations upon which they are based. It will prevent misunderstanding in criticism, and the disappointment incident to application of the suggested remedial measures to improperly chosen clinical cases.

Our studies [2] were made originally with an eye to analyzing in the terms of colloid chemistry a series of physiological and pathological phenomena which are associated with the problem of water absorption, and with no immediate ideas of applying clinically any of our deductions. We think that we have succeeded in showing that the water of the body cells and fluids is carried as hydration water in combination with the hydro-

[1] See page 540.

[2] For references to them, see the bibliography at the end of this volume.

philic, more especially the protein colloids found in them. We have extended this view to include œdema, which we have defined as a state in which the hydration capacity of the body colloids is abnormally increased. As causes of œdema we have cataloged any substance or condition which is capable, under the circumstances existing in the body, of increasing the hydration capacity of any of its hydrophilic colloids. We have mentioned that an abnormal production or accumulation of acids constitutes one of these conditions, but in spite of its dominant rôle we have never maintained this to be the only one. As we discovered that all salts, including the neutral salts, decrease the hydration capacity of certain proteins swelling in the presence of an acid, it is but natural that we should have insisted that use of such a fact could and should be made in combating the increased hydration which in the body we call œdema. And since such an œdema, as it involves special cells, special organs, or the body as a whole, goes by many names, it is only natural and logical that we should have proposed the same principles for the treatment of all of them.

Upon such considerations, learned in the laboratory and upon animals where alone we can obtain strictly reproducible results, is based all that we have tried to formulate into some principles that should guide us in the treatment of those clinical conditions in which an œdema is a prominent feature, and independently of whether it involves the whole body or individual organs like the skin, mucous membranes, kidney, brain, liver, eye, or optic nerve.

I do not believe that these fundamental propositions have been or can be validly attacked. Progress will be furthered by those who make the more positive contributions which tell us *how* chemically or physically conditions are brought about in any organism which alter the hydration capacity of its constituent colloids. In this problem, as always, science will be moved less by the cry of what is not, than by the whisper of what is.

PART EIGHT

APPENDIX

PART EIGHT

APPENDIX

I

THE RELATION OF MOUTH INFECTION TO SYSTEMIC DISEASE [1]

1. Introduction

I am sure that the medical profession has never pressed home the importance of good teeth and their preservation as effectively as has the dental profession. In fact, the dentists have succeeded so well that it is at this time almost impossible to find a patient who will submit to an extraction or a dentist who will do it. I am not here to urge a return to pristine methods. The only question that I am going to discuss is that of whether we have allowed the pendulum to swing too far. We do not want to go back to the age when we lost our teeth easily. On the other hand, from the very fact that we do not now do so, a serious new problem has arisen. Is the mere preservation of the teeth to remain the first consideration, or does not this in many instances become a menace to our general health? To the discussion of this more modern question the dentists have also contributed much. They have told us times without number how close is the relation between unclean mouths, between diseased conditions about the teeth and systemic disease, but because their proofs have rested so largely upon clinical evidence alone not everyone has been convinced. In clinical observation so much depends upon the judgment of the observer, and there is always so much slippery ground, that the conservatism which makes most of us skeptics is in good part justified.

It marks a great step forward that a number of scientific

[1] Republished with additions from the stenographic report of an address first given to the Cincinnati Dental Society, January 29, 1915, and first published in the Dental Summary, **35**, 607 (1915).

researches fathered by that master mind in medicine, FRANK BILLINGS,[1] and worked out in their clinical, bacteriological and therapeutic aspects by his associates and assistants have brought unequivocal proof for what many dentists long suspected and what some medical men have taught, namely, that there is a most profound relationship between certain diseased conditions about the mouth and systemic disease. Now, why is this question, as a general problem in medicine, so important? The answer is, I think, found in the following:

Within the years that all of us have been working in medicine we have seen two great changes come over the world. First, we have found the average length of life per individual gradually to increase; second, we have seen the causes of death decrease in certain categories while increasing in others. There is, for example, an agreeable falling off in the deaths due to typhoid, to cholera, to small-pox; an increase, on the other hand, in the number of heart and kidney deaths, of those due to arteriosclerosis, and of deaths due to certain other causes too frequently regarded as the necessary accompaniments of "old age." We shall return to this problem later but even here I should like to emphasize that old age is, in my opinion, not so much the cause of these pathological changes, as these are the cause of old age. There is a physiological death, but I question very much, judging simply from the people and patients that I have seen, whether this ever occurs below ninety or a hundred years. But if we no longer die of the old causes—and we do not—then what is it that does carry us away in our forties and fifties and sixties? Barring gross accidents and such things as cancer—of the true nature of which we as yet know almost nothing—we now die very largely of the direct or indirect consequences of low grade infections, the nature of which is only just becoming clear. And since these infections must have a beginning and must come from somewhere, and since a part of this somewhere is in the mouth, as we shall see, we have every reason to feel an interest in this discussion.

The truth of all this will come home to you more clearly as we proceed. We do not die of acute scarlet fever, of acute typhoid, of

[1] FRANK BILLINGS: Arch. Int. Med., **4**, 409 (1909); ibid., **9**, 484 (1912); Jour. Am. Med. Assoc., **61**, 819 (1913); ibid., **63**, 899 (1914); Forchheimer's Therapeusis of Internal Diseases, **5**, 169, New York (1914); Focal Infection, New York (1917).

acute pneumonia, as much as we used to, but most do not yet die physiologically. In our city, for example, there used to be several hundred typhoid victims with many deaths every year; and now we can hardly find one to demonstrate to our medical students. But consider for a moment the necessary corollary of all this. Evidently those who have been spared from typhoid are saved up for death by another cause, and it is for us to ask what these newer causes are. The present-day point of view in medicine is on this account alone a totally different thing from what it was a score of years ago, for our medical problems, in their quantitative relationships if in no other, are now totally different from what they once were.

And yet we shall observe that even these newer deaths are still attributable to the enemies that harassed us before, only they are less virile. The victims still die, in other words, of infections, but they are subtler in type. Where do these subtler things come from? They are systemic infections very largely, as we shall find, but they spring from local causes, which, because they are at times very small, have been and still are largely overlooked.

2. Historical Remarks

The so-called specialists in medicine have, of course, frequently called our attention to the close association between disease in particular divisions of the body and disease elsewhere in the organism. Thus, the aurists and rhinologists have long emphasized the important relationship between infections of the ear or nose and infections of the brain and its meninges. The gynecologists have long known that infections spreading through the fallopian tubes are the frequent cause of local or generalized peritonitis, while infections of the uterus are commonly the source of generalized infections. A great many women, for instance, who do not die of the acute childbed fever so common years ago, still die of this but in the subtler form which is all too frequently overlooked. Subacute infections starting in the lacerated uterine tissues may spread into the circulation to move with the circulating blood throughout the body. It is just such types of low-grade infection that we are going to discuss. The genito-urinary specialists have also noted the important relation existant between infections of the organs with which they deal and systemic disease.

I remember when the gonococcus was first recognized as capable of giving rise not only to a local infection, but to a systemic one as well. From a local focus the gonococcus may spread into the general circulation thus yielding ultimately, if the organism locates in the heart valves, an endocarditis, or, if it locates in the joints, a so-called gonorrheal rheumatism.

The dentists, too, have taught us many lessons in this regard. They have repeatedly emphasized the important connection between trouble in the mouth and systemic disease. WILLIAM HUNTER, in England, preached this lesson, and none ever did it better than M. H. FLETCHER of our own city. FLETCHER was the first to convince me that a diagnosis of trifacial "neuralgia" never meant anything. Of course, some medical men had suspected this in some cases, but most held then and some still hold, to a neuralgia *sui generis*. Well, neuralgia means pain in a nerve, and is just as complete a diagnosis as headache or toothache. The time has come when we are justified in raising our eyebrows and praying for the patient whenever a doctor diagnoses a case as neuralgia and stops content. The neuralgia is a symptom expressive of pathological change in the involved nerve, due to intoxication or a true inflammation, and many a one as it involves the nerves of the face is but the expression of an intoxication or an infection, traveling up the fifth nerve from a bad tooth.

Of thirteen cases of trifacial neuralgia which FLETCHER studied, he relieved twelve by proper treatment of infections about the teeth. I like to compare with this record that of some of my surgical friends, who have handled the same distressing condition in other ways. A popular method with them is to pull the fifth nerve out by the roots. In other words, the telephone bothers them, so they rip out the line. They have other ways also of handling the situation. Instead of recognizing the origin of the trouble and locating it (as is commonly the case, in the teeth) the surgeons kill the nerve, or paralyze it with alcohol.

3. Infections of the Blood Stream and Systemic Disease

The researches of the last twenty years have slowly forced home to us the enormous number of times that we get, in various diseases, infections of the blood stream, in other words, states in which showers of micro-organisms invade the circulating fluids of the

body. We used to think that everybody thus attacked, in other words, every victim of a bacteremia, was doomed to die. When I was a medical student—blood cultures were just becoming common then—a positive finding was practically synonymous with a fatal prognosis. We have gotten over that notion, and as our methods for discovering bacteria in the circulating blood have improved, we have gradually found a whole list of infections in which there is at some time in the period of the disease an invasion of the blood stream.

One of the first in which such invasion was recognized was typhoid fever. Originally, the typhoid bacilli were cultivated from the feces. They were next isolated from the Peyer's patches, and at this time it was quite generally held that typhoid fever was essentially a disease of these patches from which soluble toxic products spread into the circulation to produce systemic effects. But soon the typhoid organisms were isolated from the urine, from the rose spots, from the saliva, and finally, from the blood itself. When the blood itself was found invaded, it ceased to appear strange that the typhoid organism might be isolated from any of the organs and all the secretions of the body. Our conception of typhoid fever thus changed completely from that in which it was considered a local disease of the Peyer's patches with systemic toxic effects, to one in which it was regarded as a systemic invasion with typhoid bacilli, from which various local evidences of disease might arise. Localizing in the lymphoid tissues of the body, it gives rise to the swollen and ulcerated Peyer's patches and to the enlarged spleen; localizing in the skin, it gives rise to rose spots; passing through the kidney, it may yield evidences of a nephritis.

Shortly after these discoveries were made, similar facts were found true of the pneumococcus. We used to think that lobar pneumonia was essentially a disease of the lung, and as starting here. But as these patients were examined more carefully, it was found that the organisms responsible for the lobar pneumonia not infrequently circulated in the blood. With improved methods of examination it was soon found that practically every lobar pneumonia victim had the pneumococcus circulating in the blood at some time in the course of the disease. We have in consequence largely given up the old inspirational theory of lobar pneumonia, and now regard it more as a disease which is in essence an invasion

of the blood stream, with marked local manifestations in the lung.

The same general truth was brought out for plague, by our fellow-citizen, WILLIAM B. WHERRY.[1] We used to distinguish sharply between the pneumonic type of plague (which we held to be due to inspiration of the plague bacillus) and the bubonic form (which we held to be consequent upon the introduction of the organism somewhere into the lymphatic streams of the body. WHERRY was able to isolate plague strains, which, when injected into the general circulation of animals, would localize in the lungs, in one group of instances, and give the animals a pneumonic plague, while in another, they would localize in the lymphatic tissues and give rise to a bubonic form. In other words, blood infection is really common to both; the peculiar manifestations of the disease depend upon the type of organism, this in its turn determining which clinical expression of the disease shall spring from the general blood infection.

The subject before us deals with this same problem of blood stream infection and tissue localization, though the organisms which we shall discuss will be of a more ordinary variety. For the most part our remarks refer to the streptococcus, though several if not many other types of organism will shortly be found to belong in this same category.

What, in the first place, is the character of the infectious organisms which invade the blood stream to give rise to the disturbances to be discussed? Generally speaking, they are of a rather low grade of virulence. Applied to the specific example of the streptococcus group of organisms, this means the following.

The streptococcus that we learned to know as students typified the most virulent of the various infections that harass mankind. We used to describe the symptoms following infection therewith as of sudden onset and characterized by high fever, great prostration, high leucocytosis, and, very frequently, early death. At least a part of the "hospital gangrene" of the Civil War was of this streptococcic type, which would go through a hospital like fire and burn out every ward in it. There is a great difference between this old picture and that of the streptococcus as we know it to-day. We now know streptococcus infections which show no fever, no leucocytosis and only a moderate invalidism. It must,

[1] WILLIAM B. WHERRY: Personal communication (1906).

however, be clearly remembered that if we look sharply enough, we will frequently find even in these aberrant cases many things to help toward a correct diagnosis. Between the two extremes there exist all possible transitional types. Patients with these low-grade infections are commonly of the ambulatory type. They have days of acute illness, of "biliousness"; they may be filled with aches and pains; they drag along for weeks, months and years, never very ill, but never well either. They are often anemic, frequently adjudged neurasthenic, many times hypochondriacal. In this way they may live out what looks like their allotted number of days, though not infrequently the more spectacular manifestations of a gastric hemorrhage, of gall bladder disease, of appendicitis, of endocarditis or an acute kidney attack may close the scene.

What has happened to the streptococcus we used to know that permits it to play these new and varied rôles, for, as we shall see, it is still this organism that is chiefly responsible for the clinical pictures we have drawn? The organism, because of changes in its environment, has changed many of its old-time qualities. Instead of the one streptococcus we used to know, we now recognize a whole family of them which vary in their properties, from those practically avirulent to such as are of classic type, with the high virulence that we have already discussed.

4. Modification of Micro-organisms through Environment

This question of the modification of the qualities of micro-organisms through environment, has also received detailed study only in the last years. It is a little appreciated fact that our colleague, William B. Wherry, is again responsible for what are the most fundamental contributions in this field. Some fifteen years ago, he showed that the cholera-red reaction which is typical of the spirillum of this disease depends upon the kind of medium in which the organism is grown.[1] If it cannot produce a nitrite out of the medium in which it lives, this so-called cholera-red reaction does not develop. Here we have the development of a certain substance giving rise to a typical bacterial reaction, dependent absolutely upon the nature of the culture medium in which the organism is made to live.

As familiar to you, there occasionally appear in tubercle bacilli

[1] William B. Wherry: Jour. Infectious Dis., 2, 436 (1905).

what are called "spores." They are not true spores, but they are called such because they look like them. Their development also depends upon the character of the medium in which the micro-organisms are grown. WHERRY [1] has been able to produce the "spore"-bearing type of tubercle bacilli and the ordinary form at will, by simply varying the composition of the culture medium. Still more interesting, he has also been able to vary that property upon which depends, under ordinary circumstances, the very recognition of the tuberculosis group, namely, their so-called acid-fastness. The tubercle bacillus after being stained by certain dyes is not decolorized, as you know. This acid-fastness can be varied at will, depending upon the kind of medium in which the tubercle bacillus is grown.[2]

Most startling, perhaps, is the fact that WHERRY has controlled what in biological terms amounts to a change of organism from one class into a totally different one. By alterations in the surrounding medium he has made certain amebae (familiarly known to you as gelatinous masses crawling over a slide) change into free swimming, flagellated organisms and back again—a most remarkable piece of work. These accomplishments of WHERRY [3] mark the most tremendous variations in a biological sense that have ever been accomplished by external means in any group of organisms.

We turn now to the studies of E. C. ROSENOW, who, by special methods of isolation and growth, has produced marked variations in the members of the streptococcus family. While these studies are less striking in a general biological sense, they are most significant in their practical bearings upon the every-day problems of health and disease. Some years ago, we recognized as fixed forms the old streptococcus pyogenes, the streptococcus longus and the streptococcus brevis—all varieties of pus formers; then we had listed also the streptococcus erysipelatis, a short chained affair occurring in erysipelas cases; to these was added the streptococcus rheumaticus of POYNTON and PAINE,[4] isolated by them from acutely affected rheumatic joints and a little different in morphology and behavior from the other types. To this already long list,

[1] WILLIAM B. WHERRY: Centralbl. f. Bakt., Parasitenk. u. Infektionskr., **70**, 115 (1913).

[2] WILLIAM B. WHERRY: Jour. Infectious Dis., **13**, 114 (1913).

[3] WILLIAM B. WHERRY: Arch. f. Protistenk., **30**, 77 (1913).

[4] F. J. POYNTON and A. PAINE: Lancet, **2**, 861 (1900); Brit. Med. Jour., **1** (1904); Lancet, **1**, 1524 (1910); ibid., **2**, 1189 (1911).

came another streptococcus, which, because it forms green patches on media containing blood, is known as the streptococcus viridans. As it is commonly obtained from the vegetations of endocarditis, it is also known under the separate heading of streptococcus endocarditidis.

One of the important contributions of ROSENOW [1] to this whole subject has been his demonstration that these various streptococci, including the so-called pneumococcus, are related and that it is possible to change the typical representative of any one of these classes into a totally different one at will. In other words, a streptococcus known by one name in one place can, by proper cultural methods, be changed into another type. The important thing to be kept in mind is that such changes in culture ground occur not alone in the cloistered atmosphere of our laboratories, but daily in nature. In other words, an organism like a streptococcus living an avirulent existence in some neglected point of our anatomy, may any day become the progenitor of a highly virulent family with mutilating and death-dealing properties, if only its surroundings be slightly changed.

Let it be emphasized that these changes in environment are occurring constantly in our bodies, and often in very small areas. To give a concrete illustration and one that fits our interests tonight, it may be emphasized that the mere pulling of a tooth, with the trauma incident thereto, may so change the environment that what was a perfectly innocuous type of infection is converted into a virulent one, which may kill a patient. And why? Simply because the trauma may so affect the circulation through the tissues that where once there was plenty of oxygen there is now little or none, in consequence of which an organism which previously grew as a mere saprophyte now changes entirely and to the disaster of its host.

5. Fundamental Systemic Pathology

But not only has ROSENOW demonstrated how from one type of streptococcus others may spring, he has also shown how their pathological effects are in essence all produced in the same fashion. Nearly all these systemic effects, by whatever name we are going to call them later, are due to the fact that the organisms involved

[1] E. C. ROSENOW: Jour. Infectious Dis., **7**, 410 (1910); ibid., **14**, 1 (1914).

get into the general blood stream and while floating in this get caught somewhere in the smallest capillaries, supplying different portions of our bodies. And, depending upon the particular "affinities" of the organism and the location of the capillaries in which they are caught, these infections give rise to a whole series of different clinical manifestations to which very different clinical names have been, and are, attached. In other words, following their entrance into the blood stream from any focus whatsoever these micro-organisms ultimately give rise to the phenomena of infectious embolism. Only, depending upon the organ struck (in its turn, but the expression of accident and the particular type of organism involved), we get totally different clinical manifestations. Unless as doctors we see the whole patient and understand what has been and is happening, we can do little to help, even though we send for half a dozen specialists to reach each of the organs that may be involved. We do not need the specialists half so much as one man who will find for us the open door through which the infection has been or is entering, and from which pathogenic organisms are being sown broadcast into different organs.

After an infection has broken into the blood stream, where may the organism localize, and by what clinical name is the localization likely to be designated?

The infection may localize in the *heart valves*. We used to be taught that to produce a valvular endocarditis bacteria floating in the general blood stream reached the valves, stuck fast to them and then produced the set of inflammatory changes which we call endocarditis, and which clinically, give rise to the signs and symptoms that some call valvular heart disease. Rosenow [1] has shown that this notion is wrong. As you know, the heart valves themselves have practically no blood vessels in them. These run in the body of the heart muscle; and at the places where the valves are located the capillaries simply loop and dip into the fixed bases of the valves. It is the bacteria floating in the blood passing through these capillaries at the base of the valves and arrested here that give rise to the original lesion in valvular endocarditis. In this locality the oxygen is not plentiful and so the bacteria are likely to develop virulent characteristics which originally they may not have had at all. The endocarditis thus started

[1] E. C. Rosenow: Jour. Infectious Dis., 7, 410 (1910).

at the base of the valve may gradually involve all of it and finally, perhaps, destroy it.

Just as the micro-organisms floating in the blood may localize in the tiny end arteries of a heart valve, they may also come to rest in a *muscle*.[1] The usual spot chosen is where muscle joins tendon, for it is here that the circulation is least perfect. Since this is synonymous with the least adequate supply of oxygen, it is not surprising that here the micro-organisms do their greatest mischief. What has been described is the mechanism by which muscular rheumatism is produced. Incidentally it also becomes clear why rheumatic pains and the tenderest points in this disease are located so frequently not in the bellies of the skeletal muscles, but at the junction points between muscles and tendons.

The same changes that appear in skeletal muscle may appear in *heart muscle*. Through the described embolic infection we obtain an understanding of the origin of many types of myocardial disease.

As you know, the linings of *joints* are also supplied with end arteries. They penetrate the synovial membranes and make a loop in them. Bacteria may localize in these loops and when this is followed by the ordinary inflammatory and proliferative changes characteristic of such infection, they give rise to small destructive lesions. Briefly put, small infarcts are produced. Usually they are anemic, but if bleeding occurs the infarcts become hemorrhagic in type. In either case, a destruction of the involved area is common. When these things happen we have before us the fundamental pathology of a so-called joint rheumatism. If the process occurs like a bolt from the blue we call it acute articular rheumatism. When it is less acute, it becomes chronic articular rheumatism. If it is very slow in its progress and involves not only the tissues of the joint itself, but also those about it, and we have in consequence in close proximity evidences of an atrophic and a hypertrophic type of inflammatory change, we call it arthritis deformans. Let me add that, in my opinion, many such cases are also called gout.

These infectious embolic processes may occur also in the blood vessels of the *skin*. This marks the origin of many different types of skin eruption. One type that Rosenow has been able to reproduce in animals by injecting certain streptococcus strains is the so-called herpes zoster; another erythema nodosum. What

[1] E. C. Rosenow: Jour. Am. Med. Assoc., 60, 1223 (1913).

tyrants words are! How often have not patients come to us, told us that they had red and swollen patches somewhere about their persons, and we have sent them away satisfied after translating what they told us into Greek and Latin!

But not only may micro-organisms circulating in the blood localize in the heart, in the muscles, in the joints or in the skin, they may do this in the capillaries of the *kidney*.[1] When this occurs, it marks the origin of certain types of nephritis. These are commonly called BRIGHT'S disease, though this name ought really to be reserved for those kidney changes which are associated with arteriosclerosis. If, however, every circumstance that yields albumin and casts in the urine is to be called by his name then a streptococcus, staphylococcus and many another type of infection of the blood stream constitutes one of the possible ways of getting BRIGHT'S disease. The infectious emboli commonly locate in the glomeruli (glomerular nephritis) but they may also come to rest in the capillary beds about the convoluted and straight tubules (tubular nephritis). In consequence of the tiny infarcts thus produced, spot after spot in the kidney is eaten away. As the spots die, albumin and casts appear in the urine. The amount of such spotty involvement may, of course, be very general and occur very acutely; or it may be very local and slow-going, but nevertheless progressive in type. Depending upon which prevails we have either an acute or a more lasting, chronic, type of nephritis.

As already indicated, it is after a primary involvement of the blood stream with micro-organisms from what may be by itself an insignificant lesion that the *lungs* may become the seat of a localized infection, not only in the striking form of lobar pneumonia, but also in the patchy form of lobular pneumonia. And these pulmonary infections may be decidedly acute in type, as is so commonly the case, or chronic.

To this already long list of clinical entities, behind which lie as we now know embolic infections of various kinds (particularly with the streptococcus), there must be added some types of *thyroid* disease. Many of these are really infections of the thyroid gland, secondary to a blood stream infection originating in some neglected focus elsewhere in the body, as in the teeth. The first time this

[1] E. R. LE COUNT and LELIA JACKSON: Jour. Infectious Dis., **15**, 389 (1914); GEORGE F. DICK and GLADYS R. DICK: Jour. Am. Med. Assoc., **65**, 6 (1915).

was told me, I confess that my confidence in the world's sanity was shaken a little. Had not everybody taught us that hyperthyroidism was "metabolic," "idiopathic," "physiological" and all that sort of thing—fine words with which to stupefy us and keep us stupid?

The gospel of infection was preached to me by ROLLIN T. WOODYATT,[1] who called my attention to the practically constant association of "goiter" in patients with mouth infection. In one morning, he showed me five patients with typical signs of hyperthyroidism (tremor, cardiac attacks, eye signs, etc.) in every one of whom there was well-marked infection about the teeth. With my lesson learned it was no trick in the next two days to find three goiter cases among some patients of my own, and to observe that all had dirty mouths. To these clinical observations, ROSENOW [2] has added experimental ones. He has isolated streptococci from human thyroid victims which, when injected into dogs, produce the signs of hyperthyroidism.

Whenever new light is found it is of interest to look back and see who in the army of the past saw best with the candles that were once supreme. The French clinicians frequently emphasized and commented upon the many similarities between the signs and symptoms of hyperthyroidism and those of acute rheumatism. In acute rheumatism there is a tendency to sweat, a loss of flesh, a tremor and a hyperirritability of the central nervous system, which are also, as you see, the signs of hyperthyroidism. Last summer while going through the library in an idle moment, I took down GRAVES' monograph on the disease which bears his name. The clinical details of his first case show this to have been one of hyperthyroidism in a woman convalescent from acute rheumatism. But acute rheumatism is now but the clinical name for a streptococcus infection of a certain type.

But not only has it been possible in the instances thus far cited to work out clinically the connection between recognized bedside pictures and certain infections, to isolate the organisms concerned, and with them, to reproduce in animals the clinical pictures from which the organisms were taken originally, but it has also proved possible to do this in the case of *gastric and duodenal*

[1] ROLLIN T. WOODYATT: Personal communication (1914); see also FRANK BILLINGS: Jour. Am. Med. Assoc., **63**, 899 (1914).

[2] E. C. ROSENOW: Personal communication (1914).

ulcer,[1] *cholecystitis with stone*,[2] and *appendicitis*.[3] In other words, gastric and duodenal ulcer is the product of an infectious embolism involving a larger or smaller patch of the mucous membrane in stomach or duodenum. The same is true of cholecystitis. Rosenow has isolated from the walls of infected gall bladders and from gall stones, strains of streptococci which, when injected into the circulation, produce a typical cholecystitis, in the course of which tiny gall stones may be seen to begin their development upon the surface of the inflamed mucous membrane lining the gall bladder. It is a fact of great interest and one in keeping with the general idea of the embolic nature of these infections, that such cholecystitis cannot be produced by injecting the streptococci into the portal circulation, but only by injecting them into the systemic. Similar statements may be made regarding appendicitis. Organisms isolated from the walls of infected appendices will on injection into the general blood stream, reproduce the disease. It is certainly remarkable that we get appendicitis, on the best evidence now available, not through an infection which travels from the bowel, for example, into the lumen of the appendix, but from micro-organisms circulating in the arterial blood which have gotten into this from some distant focus of infection.

Once we get these things clearly in mind, it becomes evident how entirely inadequate is the mere diagnosis of stomach ulcer, of gall bladder disease, of gall stones, of appendicitis even. True, these are local manifestations and such as fill by their acuity and immediate dangers our entire consciousness, yet, if we remember their infectious origin and that this infection got in somewhere, how important becomes the problem of discovering where this somewhere is!

To these observations needs now to be added one by William B. Wherry[4] which is destined to play an enormous rôle in our future concepts of disease. Wherry has shown that many patients suffering from local infections, as about the teeth, get and have periodic sowings of bacteria into their blood streams and, apparently, *without developing therefrom any localizing symptoms whatso-*

[1] E. C. Rosenow: Jour. Infectious Dis., **19**, 333 (1916).

[2] E. C. Rosenow: Personal communication (1915); Jour. Infectious Dis., **19**, 527 (1916).

[3] E. C. Rosenow: Jour. Infectious Dis., **16**, 240 (1915); ibid., **18**, 283 (1916).

[4] William B. Wherry: Personal communication (1914).

ever. It will be interesting to discover how many of the down-and-outers and bums that frequent our city institutions are really the victims of such infection, and how many are constitutionally worthless. Our hearts should not bleed too easily for the really unfit, but I confess to being moved by Petri plates showing scores of colonies of the streptococcus family, cultured from the general blood stream of patients, who, on careful clinical examination, show nothing but bad teeth and sore gums. Let me emphasize that many of the patients studied by WHERRY were not bedridden, and were in the hospital for minor ailments. Many would be regarded as mere loafers; most were "unfit" from the standpoint of industry. As a matter of fact, they were ill. This type of infection is unquestionably common beyond anything we estimate at the present minute. It is responsible I think for much that is called "autointoxication," "migraine," "dumb gout" and is the real cause of many an anemia. Whence come the pasty-faced individuals that fill our cities? Many, if not all, are the victims of low-grade systemic infections of a very chronic type.

The world is full of these people who are not overly well. If they are over forty their infirmities are commonly laid to the menopause, or to oncoming or established "old age"—things which, of course, express nothing more clearly than our ignorance. To assign things to old age explains nothing; we need then to explain old age. And here much light is going to come to us soon. Conservatively, I think, half the things that we to-day attribute to old age are really the things that make us old. As has so frequently happened in medicine, we have gotten cause and effect hindside to. Is not arteriosclerosis, for example—or, as I prefer to call it, vascular disease—caused by old age? Were it, then why will so many of the really aged persist in carrying soft and unscarred arteries into the grave; and why, on the other hand, will some men in their twenties, some in their thirties, and great crowds in their forties, begin to show the evidences of disintegrating circulatory systems? Is it not more probable that the bad system of pipes determines the premature old age, and not the other way about? If this seems reasonable, then whence come the vascular changes? Whenever we are ignorant of the etiology of disease, particularly chronic disease, we lay it at the door of man's vices. And this has happened for arteriosclerosis as for other obscure things in medicine. The only trouble is that on looking about,

one observes the most virtuous dying of this thing. The worst arteriosclerotic I ever saw was a middle-aged, well-to-do, industrious farmer, who worked moderately every day in the California sunshine, who used no coffee, tobacco or spirits, and whose personal life was so exemplary that people of his valley called him "Ernest the Good." In other words, there are people who do not overwork or overworry, who avoid all foods that are worth eating, who never use coffee but drink its horrible substitutes, and yet all this gets them nothing in the way of freedom from vascular disease. Please understand me correctly in this matter. I am not maintaining that excesses in some of these directions may not be bad for the individual who *has* vascular disease. I only want to emphasize that there is no evidence at hand to show they caused it.

The reason I say this so emphatically is because this old guard of alcohol, tobacco, coffee, lead poisoning, hard work, meat diets, etc., all represent general types of intoxication, in other words, they represent intoxication with a soluble poison circulating through an organ. But we do not know any such soluble poisons, which, when experimentally or otherwise introduced into an organ, will involve only parts thereof. When arsenic, or lead, or phosphorus, circulates through a kidney, a liver or a heart, it affects the whole quite uniformly. This holds true for the blood vessels, too. A soluble poison like a dilute alcohol cannot circulate hour after hour through the blood vessels and only injure patches in them. Yet, vascular disease (arteriosclerosis) is a patchy disease and no matter how advanced, is never seen to have involved all portions of the blood vessels. The patches of vascular disease as seen in the larger blood vessels really begin in the areas about the vasavasorum. In other words, vascular disease begins in, and is essentially a disease of, the smallest blood vessels. When it attacks the large blood vessels, it really does so only indirectly by affecting the small blood vessels which supply the coats of the large with nutriment.[1]

We have known for many years that in an enormous proportion of the arteriosclerotics (in something like 60 per cent of them according to certain authors) an organism is responsible for these focal changes in the blood vessels, namely, the treponema (spirochete) of syphilis. The essential changes are again those of infectious embolism, involving the vasavasorum. In the remain-

[1] See page 634.

ing 40 per cent (and probably mixed in as secondary invaders with many so-called syphilitic ones), we will unquestionably find other organisms constituting the emboli from which follow the pathological consequences that yield us ultimately the picture which, pathologically, we call vascular disease, and clinically, arteriosclerosis, or what you will.[1] The infectious embolism is again followed by infarction, by partial attempts at regeneration, by more definite evidences of degeneration, the whole capped, maybe, by a deposition of calcium salts. And following these changes in the blood vessels, as they involve different organs, we get that whole troupe of "diseases" so likely to fill our later days. There may be hemorrhages into a vital organ like the brain or medulla; or a slower shutting off of the blood supply with mental deterioration, stupor, coma and death; or portions of the kidney may gradually die, giving us a chronic Bright's disease; or the changes may involve the heart and we die of a myocardial degeneration; and so on *ad infinitum*, just depending upon where in our bodies this blood vessel disease shows its hand most conspicuously.

I have given you now a very long list of "diseases" at the causes of which we could only guess a few years ago, but which to-day we know definitely to be due to infection. The matter is no longer one of opinion or hypothesis, but of fact. But to accept this, if it has not already done so, must change our whole point of view in practice, for the bulk of medical practice is made up of the very diseases that I have listed for you. Evidently, the time is past when we may rest satisfied with the mere diagnosis and treatment of rheumatism, gastric ulcer, vascular disease. Exactly as in diphtheria, scarlet fever, erysipelas we must not only meet the obvious problem, but trace it to its source, to the end that our patient may not again become the victim of a like attack, or a menace to those near him. In all these patients we must work backwards, and discover the original point of entrance of the infection. What good does it do to treat an acute rheumatism if after we have nursed the patient through one attack he is left liable to a second, third and fourth? Because fortunate once, it does not mean that he will win always. And what is true of rheumatism is true of endocarditis, of gastric ulcer, of appendicitis, of gall bladder infection and the rest of the cate-

[1] See in this connection the vascular changes noted in rabbits by T. B. Hartzell and A. T. Henrici: Jour. Am. Med. Assoc., **64**, 1055 (1915), after the intravenous injection of streptococci isolated from alveolar abscesses.

gory. As long as the patient continues to carry about in him his original source of infection, his symptoms may recur again and again.

6. Points of Entrance for Systemic Infection

This explains why it is so necessary to discover the original source or sources. And where, pray, are they most likely to be found? The tonsils are among the most conspicuous lodging houses for these infectious organisms. They have, of course, long been the subject of uplift work by the nose and throat surgeons. I confess to having myself laughed at them but many times since have I asked for forgiveness. As a medical man, the appeal to surgery has to me much of the cry of defeat about it, but the most radical tonsillectomist is a conservative compared with me now. I have insisted on the removal of many a tonsil which some of my throat colleagues said might stay. No tonsil from which pus may be squeezed is above suspicion, and let me add that I have squeezed pus from not a few tonsils in which some of my nose and throat friends said there was none. I am going to apply this lesson to the dentists in a minute. Let me emphasize that in patients with the constitutional findings which we are discussing, especially when progressive in type, such foci of infection *must* be found. The negative reports of half a dozen specialists means nothing in these matters. Only positive findings count. I have seen Rosenow find pus in tonsils where throat men swore there was none. He has now equipped himself with dental tools and laryngologist's instruments with which he gets pus out of teeth where dentists did not see any, and out of sinuses and throats where laryngologists missed it. And the pus thus obtained is proved the source of the various constitutional signs of which the patients complain by injection into animals which develop the same pathological pictures as shown by the patients.

You see what this means. In the too intense contemplation of our particular fields of specialism, we are likely to lose sight of the whole man; and then it takes a genius like Frank Billings or Rosenow to put us on our feet again, and to teach us that a plain doctor is more important to the patient than a whole group of specialists.

What has been said of the tonsils holds also for the nose, for the sinuses of the head, for the ears. In women we must consider the

pelvis as a focus for infection, and in men, the genito-urinary tract. Infected hemorrhoids are always to be looked for; and infected points on hands and feet, as ingrowing toe nails.

This ends the list of the common places in which infections are harbored until we reach our own specialty, that of the teeth.[1] When the tonsils are out (really out), as is commonly the case in young adults, when there is no infection in the ears or sinuses, when there is no genito-urinary infection, the problem usually comes right down to the dentist. Personally, I think that this matter of infection about the teeth, judged by its established and potential consequences, is to-day the biggest one problem in medicine.

As I have emphasized previously, the gospel of the association between infections of the teeth and these systemic disturbances, has been preached off and on for many years and by not a few dentists. What gives force to these later day arguments is that proof has ceased to rest merely upon good clinical observation and medical judgment. There is now scientific proof of the truth of what these men have so long maintained. Organisms have been isolated from the systemic foci of infection—from joints, muscles, gall bladders, gastro-duodenal ulcers, appendices—and with these organisms the specific disturbances have seen reproduced in animals. And more, the organisms responsible for such systemic disease have been isolated from infected teeth (and other foci of infections), and with these the same constitutional disturbances as exhibited by the patient, such as muscular and joint rheumatism, gastro-duodenal ulcers, gall bladder infection, etc., have been produced in animals. The chain of evidence is, in other words everywhere complete.

As practical men of everyday medicine we are most interested, however, in the clinical evidence for the correctness of these things. I am not going to weary you with a recitation of case

[1] The intestinal tract (exclusive of chronic gall bladder and appendix infections) is undoubtedly a source for occasional or periodic invasions of the blood stream and so of the whole man. There is much clinical evidence for this and some bacteriological and surgical. I omit its discussion intentionally because its importance is not yet proved in the conclusive fashion in which are the others taken up. Moreover, to relegate infection to the intestinal tract is to put it largely beyond therapeutic reach and thus to make us content with the maintained invalidism of a patient. To ignore the intestinal tract is to encourage more careful search of the superficial and therapeutically more tangible regions of anatomy.

histories, but the improvement in patients when the first source of their troubles is discovered and removed is really most remarkable. Most illuminating illustrations of this kind were first detailed by the creator of this chapter of the focal infections in modern medicine, namely, FRANK BILLINGS.[1] Since then such reports have multiplied to an incalculable number. Of course there have been those who have denied the truth of BILLINGS' fundamental teachings and the improvement in patients after attention to foci of infection. But one does not need long to be a worker in this field to recognize that such judgment is a more damning index to the skill of the critics than to the truth of BILLINGS' teachings. I doubt not that the future will turn to BILLINGS' work and see in its practical results a greater release for man from his sufferings than in any other medical work that I know of in the past quarter century.

7. Illustrative Case Reports

Among the patients that I have seen, I remember one of my surgical friends who had lost all his teeth except five lowers. He wore an upper and lower plate. He used to have his faithful five "treated" by one of the best prophylactic dentists that I know, and he went regularly and conscientiously to have done whatever was ordered. After a series of minor attacks, associated with great pain, he developed a weakness of the right arm. Being a surgeon he was practically robbed of his best instrument. The pain and weakness was due to pressure upon the brachial plexus, occasioned in its turn, as the x-ray showed, by a thickening of the bony parts in the vertebrae of the neck. For three years he tolerated his incapacitated state, always in pain and constitutionally half ill. Then the five teeth were pulled. In a few weeks he got perfectly well and has remained so. The long preceding history and his maintained freedom from any of the old signs and symptoms makes it impossible to deny the definite connection between his teeth and his arm affection.

A year ago I had a man who, for two years, had been carried

[1] FRANK BILLINGS: Arch. Int. Med., **4**. 409 (1909); ibid., **9**, 484 (1912); Jour. Am. Med. Assoc., **61**, 819 (1913); Illinois Med. Jour., **25**, 11 (1914); Jour. Am. Med. Assoc., **63**, 899 (1914).

from one sanatorium to another, because of a cardiac arrythmia. He would drop certain heart beats completely. I guessed that the disturbance was due to an involvement of the so-called His bundle of the heart, and believed that a relatively small lesion might be responsible for it. At present, one can hardly imagine such a local involvement as due to anything but a focus of infection. It was incumbent, in consequence, to look for a point of entrance. I discovered as such possibilities a badly placed and infected bridge and two lower teeth that were running pus. I advised the patient to have the bridge taken off and the two teeth pulled. The man recovered completely in two weeks.

Last year also I saw a man whose story illustrates the many rôles that a streptococcus infection may play. He came to me because he had albumin and casts in the urine. He had been told that he had Bright's disease, and that his future was not an encouraging one. I learned upon examining him that he had also had an infection of the gall bladder in the past year, and this had been operated upon and drained. He had also had an acute appendicitis during this year, though not at the same time as his gall bladder infection but following it. For this he had also undergone an abdominal operation. After recovering from it he developed an abscess in the deep tissues surrounding a shoulder joint. When I examined him he still had the plain evidences of a myositis in various muscles at the points of union of muscle with tendon and he told me that his joints would occasionally swell. Except for a trace of albumin, all these signs and symptoms disappeared in a few weeks after six badly infected teeth were removed.

It is hard, of course, to consider as of any importance a dirty mouth and bad teeth, when we are face to face with the "acute surgical abdomen," or when we are damning a man's future with the prospects of "Bright's disease," but does not this simple and so common tale teach us that we ought to?

I want to be correctly understood about these clinical histories which might be multiplied indefinitely, as I have detailed them to you. They are given to illustrate how clinical experience will verify, day after day, the intimate association that exists between focal infections and systemic disease. They are not cited to show how the pulling of teeth "cures" systemic disease, even when due to the organisms located in the region of the extracted teeth. I content myself by assuring my patients that if they will

have their foci of infection removed *they will grow no worse.* It is a fact, however, that a removal of the original source or sources of the infection leads to an entire clearing up of all systemic evidences of disease in a large number of instances, improves others tremendously and leaves but very few patients without some benefit. All this is, of course, most remarkable, for the systemic disturbances of which the patients complain are due to the localization of micro-organisms in the distant organs and these are not touched when an original focus occurring in a tooth, a tonsil or elsewhere is removed. The improvement must be obtained in some indirect way. Of course, we stop by our surgery the periodic seeding of micro-organisms into the blood and so prevent new attacks and the progress of the disease. But apparently, we help in other ways too. By removing some of the infection the patient has, temporarily at least, an overplus of his antibodies, or the local reaction following extraction, etc., may stimulate a greater production of such.[1] And these give the patient a boost which helps him to overcome the infection wherever else it may be in his body.

If this close relation between infected teeth and systemic disease is granted, then the teeth assume not only from a curative, but still more definitely from a prophylactic point of view, an importance that is not ordinarily accorded them. Not that many a dentist and many of you here to-night have not always recognized and met this important problem. But if my experience in the matter is any guide, then a majority of the dental profession is not yet alive to the whole problem, and many things are still done by dentists of a type, which, far from relieving these mouth infections, actually bring them about or favor their development once they are established. It is for this reason that I am going to venture upon the dangerous ground of saying what I think ought to be done about some of these infected teeth, or rather, what should be done in order that our teeth may never become the menaces to our general health that they now are.

8. Remarks on Some Dental Procedures

The reason that I dare to speak upon this subject is because I think that the principles of science do not change just because the

[1] See Clyde Brooks: Science, **49**, 196 (1919); New York Med. Jour., **109**, 452 (1919).

things to which we apply them have names different from those in another field for which we know these principles to work. In other words, the fundamental principles of general surgery cannot be abrogated just because we choose as the special field for surgical endeavor the mouth and teeth. That may sound like cant to you, but from conversations that I have had with some of my dentist friends, they seem to think that the teeth belong in a class by themselves, and that they have nothing whatever to do with the other things that we have in our bodies.

Now, plainly put, the teeth are simply thirty-two bones in thirty-two joints. Even without adding to these the other bones and joints in the head and neck upon which the surgical dentist frequently operates, he has here almost as many joints in point of numbers as an orthopedist is asked to work upon. And dentistry is to me, when rightly viewed, just as great a profession as is this other division of medical practice that we call orthopedic surgery. But all of us will agree that we have never demanded of the dentist (as we have every right to do) the training and the skill of an orthopedic surgeon, and certainly there is a frightful gap between the principles of surgery as employed by the general surgeon or the orthopedist and these same principles as brought into play in the treatment of teeth. Yet why should such a difference be tolerated, for *the principles of which I shall speak are those which cover bone and joint surgery; and the pathological states referred to are, in plain English, those of infection,—those of osteitis, osteomyelitis, arthritis and the problem of the fate of sterile or infected sequestra.*[1]

The first thing that some dentists—please do not think that I say this of all—the primary thing that some dentists forget is that *the tooth is first, last and all the time a living structure.* The reason I emphasize this is because dentists often work upon teeth and use things on them which they would not think of applying to the skin, to the peritoneum, or to the inside of a joint. Yet their effect on both is the same. Rough instrumentation is not

[1] I have during the past several years seen many patients in association with Gustav Eckstein, Jr., whose cooperation I acknowledge with a lively sense of gratitude. Had it not been for his enduring patience, his operative skill and his sound knowledge of pathology the lessons we have learned in common would have been fewer and the suggestions regarding dental surgery and its possibilities as reaffirmed in these pages (1920) less categorical.

without its by-effects, a hot drill cooks a tooth like a softer tissue, and antiseptics, especially when concentrated, kill teeth as rapidly as micro-organisms.

I ought not to have to say that many dentists ignore the first principles of aseptic surgery but certain it is that they do. The problem is not altogether easy, for most dental procedures are necessary upon teeth already frankly infected. But where work must be done upon such the need for initially clean instruments, for their frequent change and for eternal care not to transmit infected material from one spot to another is all the more obvious.

For the reasons already emphasized there is not much gained when the dental surgeon tries to clean up an old infection or tries to cover the defects of his technic by the use of antiseptics. We have gone through this same stage in general surgery. I am serious when I say that one of the reasons why dentists generally have gotten the good results they have is because they have largely worked without any regard to antiseptic measures. Under such circumstances their grindings, etc., usually occur in *live* teeth, and as long as they are alive, they are hard to infect. This is but an application to the teeth of a surgical truth not yet fully grasped by even the general surgeons. The difference in susceptibility to infection before and after the death of cells is easily proved. When, for example, any open wound that is covered with healthy granulations is sown with bacteria (such as one of the pus formers, including the streptococcus), the chances of getting an infection are extremely small. But if at the same time that the bacteria are sown, a piece of gauze is lightly dragged over the wound so as to crush the living and growing cells constituting the granulations, pus develops within a few hours. In other words, as soon as a tissue is killed, its liability to infection is great, and this is true, whether the tissue is called skin, peritoneum or tooth. And yet, as I shall point out in a moment, many dentists kill a tooth in any of their several dental procedures and still think that they have done no serious thing. These considerations explain why in all surgery a gentle touch with soap and water cleanliness may and frequently does mean more for the patient than the most elaborate antiseptic technic applied by clumsy hands. Obviously, if the greatest resistance to infection is offered by the living tooth itself then the patient, first, needs to protect his heritage; while we, for our parts, must aid him by keeping off his teeth all antiseptics

likely to kill his living tooth cells and all the dental procedures which, like abusive cleansing methods and badly applied bands, clasps, crowns and bridges, etc., more or less promptly do his teeth to death.

But not only must we protect the tooth from such external injury (with its subsequent disastrous liability to infection) but still greater caution is necessary when working within a tooth. Many dentists "devitalize," much too readily. To devitalize means, of course, to rob a tooth of its life, and yet when I have discussed this question with dentists they have generally talked about the procedure as if it meant merely a robbing of the tooth of its nerve supply. There is a fundamental error in this view. When, on his own admission, the dentist thus robs a tooth of its nerve supply, he robs it at the same time of its central, nutrient artery, which, when not done deliberately and with a full knowledge of the consequences, is little short of a crime. The problem is analogous to the cutting off of the nutrient artery to one of the long bones, the inevitable result of which is a death of the supplied area and the formation of a sequestrum. Applied to the tooth, *devitalization means the same thing,—a death of a part or all of the inside of the tooth and the conversion of this into a sequestrum.* And the future of that tooth is the future of a sequestrum anywhere else in the body. I know that some of you will protest that this is not so and insist that the tooth still gets a second blood supply through its periosteum which may keep it alive. In the first place, such a statement is not true; secondly, were it, then a lot of the things that are done afterwards to such a devitalized tooth are of a character to assure absolutely a suspension of any nourishment that is supposed to be brought, thus vicariously through the periosteum. In other words, some dentists after killing the inside of the tooth, later see to it that the periosteum is killed also. After that the whole tooth is dead.

Now, why do I say these things? Simply because some of the commonest dental procedures, as the placing of a gold crown, does this very thing. It is the accepted procedure with many to devitalize the pulp before placing a crown. This kills the inside of the tooth, as I have already said. To get a good fit for the crown, the convex sides of the projecting portions of the tooth are ground off, which means a killing of many of the living cells in this portion of the tooth. It is generally accepted, I believe,

that the crown must fit snugly about the neck of the tooth, projecting to or somewhat under the gum line. All dentists agree that if a snug fit is not secured, infection is bound to occur. Let me insist that infection and trouble are just as certain if the crown does fit snugly. And when to secure a perfect fit, or to make good a tooth defect extending under the gum line, the dentist first strips back the gum or forces the crown deeper, what, but disaster can be expected? Under the gold, always when badly placed, and nearly always even when well placed we have dead bone and injured peridental tissues (periosteum and synovial membrane) and, as a corollary, infection. If you do not believe this, just examine such crowns yourselves. In the course of routine physical examinations, one can look at the teeth of all his patients week after week and never find a gold-capped tooth that does not run pus. I confess to having been shocked, when, on referring these patients back to their dentists, they have returned to me with the statement that their dentists declared their teeth in good order. More than one dentist has written me that the pus I observed was a "normal secretion" from the gums.

The important thing in all this is that every such crowned tooth and, of course, every other infected tooth, whether it is crowned or not, constitutes a point of infection from which any of the serious things we have previously discussed may result. Mind you, I do not say will result—Nature is very kind to us—but may. The day is coming, I think, and very soon, when a gold crown placed as I have described will not be put on any more. And when such gold crowns go, many another now popular piece of dental engineering which builds on such crowns will also pass out.

9. Some Suggestions

Since I condemn in this wholesale fashion, you will perhaps retort by asking me what I think ought to be done. As in dentistry I am entirely out of my field, I may perhaps step boldly where angels have feared to tread.

First, of course, comes the old story of prophylaxis. I know how much the dentists have done here and yet still more must be done. I confess to large discouragement regarding our ability to handle teeth conservatively once they are extensively infected. Hence, my repetition of your own estimable teachings. Everything possible must be done to keep the teeth from decaying and

the peridental tissues from becoming infected. And how is this to be accomplished?

The health of an organ is best preserved by its proper use, wherefore the injunction to use the teeth and use them hard. While their employment as nut crackers is hardly to be recommended, this is a safer extreme than that other which finds virtue in our now so universal slop diet. The teeth are bones set in joints; and bones and joints are kept in order by exercise. The teeth should be given bread crusts, toast, tough meat, meat rinds and vegetables rich in cellulose to reduce to pulp with no external aid except the saliva. There has been much written of the bad effects upon the stomach of taking fluids with meals. Every modern fact proves that the contrary is the case—gastro-intestinal secretion, digestion and absorption are all favored by large fluid intake. I am guilty of the paradox that fluid with meals is not bad for the stomach but very bad for the teeth. If it is to be consumed it should be taken between mouthfuls of food—not with them.

To this injunction is to be added that of proper brushing—brushing of gums and teeth. A new brush which tends to cut the gum because its bristles are cut on the bias may be made safe by lightly singeing the bristles with a lighted match.[1] The hardest bristles are none too hard and a brush with bristles set to taper toward the tip reaches back teeth better than the fancy forms expected to get between the teeth. The tooth brush should be used *dry*. Healthy gums and teeth may be brushed up and down—if infected, the upper teeth had best be brushed downwards only, the lower, upwards only. This massages infected material into the cavity of the mouth and not into the bases of infected gum pockets. If a dentifrice is desired dry table salt does well, or plain baking soda. Precipitated chalk may be used or milk of magnesia. Dissolved in the little saliva which flows as brushing is continued, these materials form concentrated (hypertonic) neutral or alkaline solutions which tend to dehydrate swollen gums thereby making for better circulation through them and hence a better opportunity for preserving the healthy or aiding in the repair of the diseased gum. Hence, too, the injunction not to rinse the mouth too quickly after brushing—allow the salt solutions time for action upon the gums. Prepared dentrifices

[1] I learned this from C. C. Bass and F. M. Johns of New Orleans.

containing soap, chalk, potassium chlorate or glycerin obviously work in similar fashion. The best have little direct germicidal power—had they such, they would probably be as dangerous as they are strong.

The day of the dental quack who "cleans teeth free," by way of getting what looks to him like a real dental job seems largely over. But the honest efforts of the modern practitioner really to clean teeth seem also to be largely misapplied. In the first place the dentist cannot do through a yearly sitting what a patient cannot or will not do for himself twice daily. There are times, no doubt, when the dentist may give aid by helping mechanically to remove gross deposits like tartar. But this is ticklish business. Assuming that the dentist will make no gross errors in technic (as by carrying with dirty instruments the infection from one tooth to another) it is still to be remembered that such infectious depots cannot be stirred into without possible serious consequences. Tartar deposits about the teeth are like the "stone" formations elsewhere in the body—and surgeons do not lightly scrape about in infected gall bladders, urinary bladders or the interiors of calcified rheumatic or "gouty" joints. When the dentist follows a tartar deposit below the gum margin and into the peridental membrane he is in very fact in an infected joint and mechanical procedures in this locality are then of the same importance and significance as though carried out in a knee joint. The cleansing and keeping clean of the teeth is by itself a significant job and when the public demands dental help for its proper prosecution it must recognize its importance and prove willing to pay for it just as readily as it does now for bone and joint surgery elsewhere in the body.

But suppose that in spite of all care, infection and decay has gotten a foothold either in the form of a caries involving the protruding portions of a tooth or as an infection of the peridental tissues (pyorrhea). To limit ourselves, temporarily, to the first of these problems, it is obvious that we need to grind away the affected portions and to fill; and we are going to keep on filling as long as we can; and when we cannot fill any more, or such is not best, we are going to put in inlays. And when the inlays are so large that they will not hold any more, then what? It is common to crown, but in my opinion it is far better to follow a surgical procedure to which some of my dental friends resort, namely

put in a necessary inlay and then half crown to keep the inlay in place. A half crown is the expression of good surgical principle. An inlay may even be used if the decay extends to below the gum line in a limited portion of the tooth. With the half crown, the upper tooth structure does not have to be destroyed, and, maybe even with the inlay, no devitalization of the tooth pulp may have proved necessary. This avoidance of devitalization is most important, for devitalization, because of the reasons already discussed, defeats us from the start.

When the upper half of the tooth is so badly shattered that fillings, inlays, or inlays with half crowns no longer prove adequate, then the jacket crown is to be considered. The important thing about the jacket crown is that it does not necessitate devitalization. As soon, of course, as a tooth is, or has been killed, the jacket crown is largely useless, because the mischief is now done and it does not add much to stick on a porcelain crown, for example, by the old peg method. But as long as the tooth can be kept alive it is our sacred duty to keep it so, wherefore the superior merits of the porcelain jacket crown which, well cemented upon the healthy root-remains of a tooth, expresses to me the very acme of surgical thought, ingenuity and skill. Its expense has been urged against it; but has this ever been an adequate argument in medical and surgical practice? Whatever its cost, is it not cheaper than gall stones, or appendicitis and a fortnight in the hospital?

Thus far in our discussion we have assumed that the injury or infection of the tooth has not extended through the head in such fashion as to make devitalization anything but a matter of choice. But often, at least in the light of our present knowledge, devitalization has to be practiced as a matter of necessity. Are we never to devitalize, even under such conditions? I would say, never without a full realization of what the consequences are likely to be. The future for a devitalized tooth is, at the best, that of a sterile sequestrum; at the worst, that of an infected one. And the chances for it being the latter are more than nine to one. Wherever infection and devitalization by nature or man go together I am of the opinion that the tooth might as well be sacrificed at once. If devitalization is done with intent, the double danger of infection and dead bone must ever be carried in mind. Living tissues can withstand much infection, and a sterile sequestrum, like a sterile foreign body, can be tolerated. An infected seques-

trum will not, however, stay in a tibia or in a femur; nor will it in a tooth, just because the necrotic area is small and we give the bony growth a special name.

Examination of devitalized teeth by clinical methods and by x-rays shows lesions in and about them in nearly every case. Most of these, and the most dangerous, are hidden from the casual eye. They are commonly within the tooth itself or the x-ray may show them at the root tips and about these. Moreover, not a little of such trouble may have been planted there by the dentist. The needle or burr or hair that kills or fishes out a dead dental pulp all too often carries micro-organisms into the depths of the tooth which may have been harmless enough more superficially, but which, sealed in the bottom of a cavity away from oxygen, develop pathological properties of no advantage to their host.

These remarks will suffice to show why I lay such small value also upon root amputations, arsenic and formalin packs, root canal fillings and a dozen other dental projects. Root amputations cut off the blood supply to a third, a half or all of a tooth leaving the upper tooth structures to wither like flowers whose stems have been cut below ground. Antiseptic packs, if they kill bacteria, kill as probably live tooth structure. If anything is gained it is represented by the choice between an infection in a living tissue and the substitution for this—if things come out well—of a mummified, necrotic and (possibly) sterile patch. Root canal fillings, if improperly made or of improper materials, are admittedly purposeless; but they are equally futile when made by the genius of a CALLAHAN—they are mere pourings of balsam upon the dead.

How proportionally many are the gross lesions around dead roots is shown in an interesting study of radiographs made by THADDEUS HYATT[1] who examined 2800 radiographs. Even of the 2 per cent of these with fully filled canals, 25 per cent showed destruction. And in a similar study by GUSTAV ECKSTEIN, JR. and H. GERMANN a yet higher proportion were made out, namely 75 per cent. The latter compilation shows that it makes little difference, so far as subsequent destruction goes, whether canals are perfectly filled or not filled at all. For the examination of 1950 radiographs revealed that while 75 per cent

[1] THADDEUS HYATT: Jour. Nat. Dental Assoc., 4, 594 (1917).

of entirely filled canals entailed bone destruction, only 80 per cent of those not at all filled were in the same fix.

Similar opinion covers the value of crown amputations and the future of superimposed restorative portions. Pearly porcelain tops, in solitary or in phalanx, pegged into such half dead or dead root tips, always when badly coapted and usually when well placed, spell ultimate infection with the death, of course, of anything that may originally have escaped. Such teeth may be the joy of wearer and friends, when viewed superficially; but they are whited sepulchres hiding a foul basement.

10. The Foul Breath and the Coated Tongue

Now that I have used the word "foul," let me interpose a few remarks on this whole question of foul mouth, foul breath and coated tongue. The authorities, it seems to me, who write on these subjects go too far to seek the source of such troubles. I am convinced that every such state—barring the few cases we observe in the hospital which usually concern the acutely and desperately ill—means something wrong locally in the mouth or head, usually just mouth, and about equally divided between infections of the teeth and of the tonsils. The probability that the tonsils are at fault is somewhat higher in children than in adults, while the opposite is true for the teeth. Neither rule, of course, holds absolutely, because even young children have badly infected teeth, and many adults, given to holding on to everything they can, refuse to part with even desperately infected tonsils, because they think that someone may some day discover a function for them. I look for, and thus far have not failed to find infected teeth, infected tonsils or infected sinuses in every ambulatory patient who has a bad breath or a coated tongue. To blame these things on the "stomach" or "indigestion," is to say nothing at the best and, at the worst, to lull the patient into a state of false security about himself.[1]

Perhaps some of you would now like to ask: "And is there not a relation between these foul mouths, these infected teeth, and

[1] "It might be well to note here that most of the bacteria about the teeth and in the tonsils grow better under anaerobic conditions. An anaerobic culture of such a mixed flora, made upon blood or serum agar in the absence of carbohydrates, develops the identical foul odor possessed by a 'bad breath.'"—WHERRY.

the 'metabolic' disturbances and 'constitutional' diseases like 'gout' and 'rheumatism,' of which these patients complain?" The answer very decidedly is: "Yes." Only the teeth did not attain their state through the rheumatism and gout [1] but the other way about—the infected teeth were the cause of these.[2]

Our discussion seems to have strolled from the fields of prophylaxis, fillings, inlays and crowns to the less pleasant ones of pyorrhea and its several adjectives. Let me add my protest to that of many a dentist who insists that the term is not broad enough, for the pus in pyorrhea does not always flow. Nothing would help more to clarify the whole situation than were we to ignore this term entirely and cover the whole story of peridental infection by the term dental arthritis. For arthritis is what we are dealing with and whatever we hold to be of medical or surgical importance in the meeting of the situation must rest upon what we hold to be correct medical and surgical practice for an arthritis anywhere in the body. The first all-important fact to keep in mind in this matter of dental arthritis, no matter how restrictedly or broadly the term is used, is its infectious origin. The number of infectious organisms that may be or are responsible for it, is, no doubt, several;[3] but that it is an infection of the dental and peridental tissues, that is the fundamental thing. And these infections have a beginning. It is then that most can be done to overcome them and hence the importance of recognizing the *early* evidences of infection. Every tender gum, every bleeding gum, every eroded gum, every tender tooth and the slightest evidences of pus formation at the gum line of a single tooth mean something. The red, soggy gums of the kitchen help and of the young male laborers who abhor a tooth brush are all expressive of infection and are the red flags of danger ahead. And the flag is just as red and full of meaning when the higher strata of society are attacked. The ignorance of the individuals most commonly attacked makes reform here look desperately unpromising, but we need not add

[1] For remarks on the association of "gout" with foci of infection about the teeth, see page 756.

[2] Very rarely the tooth sockets, instead of being the *first* points of infection and the sources of seed to other joints, may be infected metastatically through the blood stream (see E. C. Rosenow: Jour. Immunology, **1**, 363 (1916)). I do not stress the point because it may lead to even less being done to control obvious points of infection in the teeth than is now the case.

[3] C. C. Bass and F. M. Johns: Jour. Am. Med. Assoc., **64**, 553 (1915).

to the whole problem by having some of our professional brethren say that there is nothing wrong with these mouths. What can be done with these peridental infections? The proper use of the teeth (even though the procedure is painful), a proper brushing of the teeth as already outlined and a careful soaking of the mouth structures in hypertonic and alkaline salt solutions helps much. Under such circumstances, superficial lesions, at least, can be made to heal, albeit, at times, not without a certain amount of recession of the gum line and exposure of the dentine.

But what if the infection is more extensive? Let me confess at once to a most discouraging experience in the matter of actual results obtained and obtainable in more extensively established mouth infections upon which some of my dental colleagues have worked and by methods more conservative than extraction. Only rarely will an infection that has penetrated deeply along the peridental tissues, as to the tip of the root, clear up. Where this has happened nature points to the principle which the dentist should follow in attacking these pus pockets—they should be laid open to their tips and allowed to drain. The pocket may then clear up after a retraction of the gum edges.

Worst of all are the infections which have burrowed up from the root following infection by fair means or foul of the dental pulp itself. None of these have I ever observed to clear.

Nothing is worse for the patient (as witness the commonness of rheumatic attacks, herpes zoster, endocarditis or appendix attacks after a visit to the dentist) or more wrong in surgical principle than the commonly practiced "scaling" of such infected teeth. If the dentist could only remember, whether he be the conservative scaler who employs hand tools only or the radical who starts out with motor driven vehicles, that what he is doing is making hash of an infected joint and that what he is accomplishing is a perfect destruction of its lining membrane he would soon stop. I confess that after the work of such men I have seen the teeth assume a better appearance, the gums a less soggy look and have seen loose teeth "tighten up" a bit. All that this means is that a series of ankylosed (and functionless) joints have been substituted for a series of soggy ones. But even this advantage is small if the general condition of the patient does not improve or, as is so commonly the case, new "rheumatic" and "gouty" attacks accompany the dental work, or appear in patients who never had them before.

I have seen exhibited the usual x-ray plates which show how after such scaling new bone is formed and all that sort of thing. All this is true, but new bone formation and a little better set to the teeth is not all we want. We want freedom from infection. Bone formation and plenty of it occurs in all bones and their periostei whenever there is an infection of these structures. But a surgeon in such cases does not try to see how much of the separated and dead bone he can get to grow fast in his patient. He pulls it all out. Nor does he expect the infection to cease until he has done this very thing. When we call the dead bone a dead root or a devitalized tooth the problem is exactly the same. We need to get rid of these and then the infection will usually take care of itself.

In the patient with an established or threatened systemic infection, the important thing from his point of view does not reside in the question: "Have the teeth been saved and has the mouth been made to look better?" but rather is this: "Has the focal infection from which the systemic has arisen been gotten out of the way?"

As a last word may I comment upon a remark which is constantly made to me? Time after time one receives the report from a dentist that a tooth for which extraction has been suggested "is alive." The corollary that one is supposed to draw is that because the tooth is alive, it cannot therefore be infected. Nothing is more absurd. While dead teeth are more susceptible to infection, live teeth of course, can be infected. While a dead man putrefies of necessity, even a live one may develop an abscess. And the situation is the same for such dead and live teeth.

11. On Extraction

My remarks will I trust have served to show you why I think the only way out of many present-day dental difficulties is over the hard road of extraction. But even extraction when fully justified and consented to, needs thought in its execution. If more than one or two teeth need to come out it is well to decide at once not to extract the necessary group at a single sitting and the whole process needs to be surrounded by all the care and precautions which are customary in bone and joint surgery anywhere else in the body.

Extract one or two teeth at a sitting, especially if they are molars, and allow several days to elapse between sittings. In the interval fresh granulations cover the sockets and liability to cross infection is reduced. The best anesthetic is gas and oxygen; next best is the careful use of novocain. Objection to the latter is dependent upon the often unavoidable necessity of pushing the hypodermic needle into or through infected tissues. The teeth should be removed with the least possible trauma to mandibles or gum. Traumatized bone and torn soft tissues are fertile culture grounds for bacteria. Hence my objection to the "radical" extractionists who to-day make elaborate and useless moon shaped incisions into the gums to expose the outer plate of a mandible and then lift up this outer plate to push out the teeth laterally. The moon shaped flap invariably sloughs, the outer plate invariably dies and suffers the fate of a sequestrum, and the teeth fail to push out when most definitely in need of removal, for when dead they are anchored by scar tissue and calcification into the socket. The result is that the teeth break off or crumble and must in the end be extracted by forceps. Less total destruction is done by starting with the forceps.

If the dentist bears in mind that he is operating in the fields of arthritis, osteitis, osteomyelitis, he will see how next to proceed. Obviously infected joint linings, pus pockets and bone fragments whether of tooth or jaw had best be removed by curette or forceps at once. Bony ridges and points which will die because of inadequate blood supply may be trimmed.

A great injustice done extraction patients is an ignoring of proper after-treatment. Free drainage into the mouth should be encouraged and patients should not simply be sent home to get over their difficulties as best they may. The sockets remaining after extraction should be cleaned out daily by the dentist (preferably by mere irrigation) and the closure of the wound by soft tissue superficially before the bony portions are clean, be prevented. A good mouth wash helps much, such as a warm baking soda or table salt solution (teaspoonful to the glass). Magnesium sulphate does well and especially to be recommended is a 1 per cent sodium chlorid solution with 2 per cent sodium citrate. To touch the pockets with a diluted tincture of iodin or one of the organic silver salts is not bad, though I question whether these or other materials have any great antiseptic action. Persistently

tender regions of extraction and persistently pus discharging sinuses have in my experience always meant fractured bone, osteomyelitis and infected bone fragments (often very small) left in the operated areas.

The dental procedures which we have discussed will make for the production and the maintenance of a clean mouth. To the patient, however, never too sensitive to its opposite, the question of the restitution of his biters and grinders may seem more important than freedom from systemic disease, which raises the question of the fundamental principles that should guide us in the making of such restitution.

There is at least one thing to be said in favor of the old-fashioned upper and lower dental plates. They may be less effective for biting purposes than the remains of natural teeth, but they are clean. The long-famous bridges attached to gold crowns or built upon structures pegged into half dead root remains are evidently all things of the past. To build such structures upon half dead teeth is to invite trouble from the start, while to build them upon living teeth by methods which insure their death is a crime.

The clinics of Roach, Ash and Hinman and the writings of men like Norman B. Nesbett[1] and W. E. Cummer[2] illustrate the principles which must be followed and what, with genius, can be accomplished through partial dentures. The eternal law to keep in mind is that nothing must be placed in the mouth which will irritate a tooth or a gum line, for such wounding must inevitably be followed by infection. Bridges should therefore be of the removable type, the teeth built on saddles well fitted and bearing upon the adentulous mandibular remains. The clasps which hold such structures in place should not grasp a tooth too low around the neck or impinge upon the gum edge. Where simple clasps do not suffice, studs may be fashioned with bearing surfaces pressing against teeth of the opposite side. To get a mouth clean, to make restitution of lost teeth through partial dentures and to accomplish the whole by means which will not lead to new infection in previously sound teeth or gums—here is a problem worthy the science and skill of the best of men.

[1] Norman B. Nesbett: Dental Cosmos, **60**, 204 (1918); Jour. Am. Dental Assoc., **7**, 302 (1920).

[2] W. E. Cummer: Jour. Allied Dent. Societies, **11**, 386 (1916).

12. Concluding Remarks

Lest I be misunderstood, let me express again my regard for the splendid work our American dentists have done in the way of preaching, teaching and bringing to pass mouth hygiene, and let me acknowledge the many teeth that, I think, they have saved to the everlasting benefit of their patients. I am not opposed to any of this. What we need to decide is whether there can be reached or, better, whether there has not now been reached the point of diminishing returns in this matter of mere tooth preservation. My patients return to me from the dentist, time after time, with the statement that a peg tooth, a crown, a root, a piece of bridge work "need not come out," or that the involved tooth structures "can be saved." I know this in advance. What I would rather know is whether, at the same time, the patient can be saved. The debate is not between the relative merits of losing a tooth and saving it, but between that of the maintenance and the cure of an infection. I am not for extraction just because it is easy. I come to it as do you, as a last resort. It is not the matter of a choice between an evil and a good thing, but that of a choice between two evils. It is too often a choice between a much-desired cosmetic effect and illness or death; or a loss of some or all the teeth and recovery from systemic disease.

Perhaps the day will come when less radical measures than those which, in my experience, have alone proved availing will be the order of the day, but progress here is going to be made, not through a greater attention to the mechanical aspects of dental surgery, but to its bacteriological and pathological sides. New light will come as clinical observation and laboratory experiment bring us a better knowledge of what are the conditions which render us liable to infection, whether in a tooth or elsewhere, and of what are the means of defense which the body uses to overcome such. American dentists, like their surgical colleagues, are to-day talking too much of mechanics and too little about surgical principles. There is a lot about hammers and tongs and new methods of nailing things together and too little, it seems to me, of why we live and die.

II

DIAGNOSIS, PROGNOSIS AND TREATMENT IN NEPHRITIS[1]

(A Clinical Lecture)

I am going to show you this evening some very familiar types of patients. There will not in any case be any debate about the diagnosis, and their commonness will bring to mind the routine service of the daily practice of each of you. I am going to comment upon these patients, and in so doing, not only indicate how inadequate are our present physiological and pathological interpretations of their clinical behavior, but substitute for these interpretations some less orthodox, but I think more logical ones.

1. Œdema in the Absence of Circulation

§ 1

This young man, whom Dr. O'Connor has just presented to you, has kindly consented to stay a moment longer while I use him to demonstrate the incorrectness of our ordinary teachings regarding the nature and origin of œdema. Dr. O'Connor has just told us that, in consequence of an injury, this man now suffers a complete break in the circulation to the lower left leg. Below the knee the limb is cold and no pulse can be detected in any of its blood vessels. In the extremity itself the toes have become gangrenous and a demarcation line is found above the ankle. Now observe that as compared with his right leg, his affected left is swollen to twice the size of the normal member, and yet, so far as we can make out clinically, the circulation in most of the leg below the knee has stopped completely. We see here, then, a tremendous œdema in the entire absence of any circulation.

This finding, which you can corroborate in all types of major and minor injuries, at once does away with those teachings regarding the cause of œdema which look to blood pressure and changes in blood pressure, as primarily responsible for the production of an œdema. Pathology formerly taught us, for example, that because of an increased capillary blood pressure, liquid is forced out of the

[1] Martin H. Fischer: Lancet-Clinic, **115**, 419 (1916), being the stenographic report of a lecture delivered before the St. Francis Medical Society of San Francisco, in the St. Francis Hospital, August 27, 1915.

capillaries into the surrounding cells, and that thereby the affected cells (the limb, in this case) are made to swell.

But, as you see, we have in this patient no blood pressure whatsoever to call upon and yet we have a marked œdema. In other words, a complete absence of blood pressure seems just as effective in bringing about the swelling of a leg as an imagined increase. This means, of course, that we need to revise completely our present conceptions of œdema and to seek the cause of it in other fields. That which is undebatable in this patient's clinical picture is that his lower leg is not getting its usual supply of blood. Let us, therefore, ask what happens when we thus cut off the circulation to an organ in a warm-blooded animal. Not only does there follow an accumulation of carbonic acid in the part, but in the absence of an adequate oxygen supply (evidenced here by the bluish-purple look of the skin), there are produced in the involved tissues various other so-called sub-oxidation acids. Lactic acid is one of them.

To understand what these acids do, we must recall their effects upon protein. When gelatin or some other protein material is thrown into cold water, it swells, as you know. But if a little acid is added to the water, the swelling is enormously increased. And that is just what has happened in this patient's leg. Under normal circumstances, as in these tissues, the proteins have a certain normal capacity to swell. But when the amount of acid in the member is increased, as in this injured leg, then the proteins absorb a more than normal amount of water and there results such an œdema as we have before us.

This leg, then, has swollen, not because an increased amount of water has been forced into the tissues, but because the tissues themselves have suffered changes whereby their capacity to hold water has been increased. Because the hydration capacity of the proteins has been increased, they have been enabled to *suck* water from any available source. In the patient, this source is found in such remaining circulation as may be continuing in the upper, uninjured portions of the leg, or in the lower margins of the intact circulation remaining above the point of injury.

§ 2

What we see here as true of a local œdema is true of general œdemas as well. It is a fact, little considered but entirely true,

that the worst œdemas observed occur in the dead if only water is furnished. A man killed and thrown into the water, or a man who commits suicide by drowning, develops an œdema in spite of the fact that he has no circulation left, and of course, in consequence of this, no blood pressure, either, to explain that œdema. What happens is that after death (really because respiration and circulation have ceased and so no oxygen is furnished) the normal oxidation chemistry of the tissues becomes changed. In other words, the so-called post-mortem acids are produced and act upon the (protein) colloids of the tissues, increasing their capacity for holding water. In our patient here, the source of the water is from the circulation bordering upon or persisting in the injured tissues; in the dead man it is from the lake or ocean enveloping him.

With these facts in mind, let us pass to a patient in whom a general œdema dominates the clinical picture.

2. The "Nephritis" of Heart Disease

§ 1

This second man, a painter, forty-eight years old, came into the hospital about seven weeks ago because of a swelling of his legs and some shortness of breath. For two months previously he had had what he calls "stomach trouble," secondary, he says, to an enlargement of the liver noted by the physician then caring for him. On questioning him, we find that the gradually ascending swelling of the legs was noticeable about two months before he entered this hospital. His account, and even a casual look at him, point to the ordinary œdema of cardiac origin, so you will not be surprised to find that his earlier history and his present state corroborate this view. Four years ago this patient had quinsy. Subsequently he had several attacks of rheumatism. His joints swelled repeatedly and became red and painful.

At the present time he is unable to lie down. His breathing is rapid and shallow; we note also that it calls into play the extraordinary muscles of inspiration; his neck muscles, you see, join in the inspiratory movements. His radial pulse is 88; the pulse beats are of unequal intensity; there is a venous pulse in the neck. Examination of his lungs shows the upper portions to be clear, although the inspiratory sound is somewhat harsh. The lower

portions of the lungs are relatively dull on percussion, with distant breath sounds and decreased vocal fremitus. There is evidently a certain amount of fluid in the pleural cavities. The areas of both relative and absolute cardiac dullness are greatly increased. The apex beat is in the sixth intercostal space and a full two inches to the left of the nipple line. The upper cardiac dullness begins just below the first rib, while on the right its beginnings lie an inch outside the right sternal edge. The first heart sound has lost its booming character, and neither this nor the second is pure over any of the valve areas.

We have evidently to dò with a disease involving directly, or through dilatation, all the heart valves; and since the muscular element in the first sound is so largely lost we are no doubt right in adding to the valvular element that of insufficiency of the heart muscle itself. The history of the patient, the fact that he has occasional rises in temperature of an irregular type, the varying leucocytosis that accompanies these, together with the physical findings so easily elicited, lead us to the diagnosis of an infectious endo-myocarditis of subacute type.

§ 2

It is of importance to notice next his blood pressure. The systolic measures 125 mm. of mercury; the diastolic we are unable to read. Please bear in mind this value for comparison with some readings in other patients that I shall show you later. The physical evidences of cardiac dsiturbance with a blood pressure showing a normal systolic value, as seen in this patient, mean something totally different, so far as diagnosis and prognosis are concerned, from similar physical findings observable in patients with high blood pressure.

Besides the changes in the heart and the fluid accumulations observable in the two pleural cavities, we note the liver dullness beginning an inch above its normal height in front and extending downward to below the costal arch. The liver is palpable a full hand's breadth below the arch. Propped up in bed as he is, we discover also that the lower tissues of his abdomen, back and buttocks are swollen, and percussion shows a ring of dullness in the lower abdomen indicative of fluid here. For these ascitic accumulations he has been tapped several times. We note, too, that his legs are heavily swollen from the feet up to the hips.

We have before us a man with a central pump which is no longer doing adequately the work it should do in pushing the blood around his systemic and pulmonary circuits. We need not debate in detail the exact character of the changes that have occurred in his heart. There are the obvious evidences of valvular defects, as betrayed by the murmurs, and of changes in the co-ordinating and muscular structures of the heart itself as shown by the irregularity in the number and intensity of the heart beats and the pulse, and by the decrease in intensity of the muscular element on listening to the heart sounds. Since the now classical pathological and bacteriological study of these hearts by E. C. Rosenow, we know them to be suffering from infection—secondary for the most part to such neglected foci as are represented by this patient's tonsils—which may involve the valves, the heart muscle, the pericardium, or all three. It is such a general involvement, in other words, a pan-carditis, that this patient shows.

§ 3

Let us ask now concerning the nature and the origin of the various clinical signs seen in this patient and so commonly observed in all bedridden cases of failing heart. Why, first of all, is there a general œdema? In consequence of the incompetent valves and in consequence of the decreased contractile force of the cardiac muscle, this patient is not pushing his blood stream through his circulatory tubes at the normal rate. What must be the consequence? All the tissues of his body will suffer from two things—first, the carbonic acid produced normally in all living cells will fail to be removed from them as rapidly as it should be, and second, the cells will be inadequately supplied with oxygen. In other words, there must occur and has occurred in practically all the tissues of his body, what we observed in the leg only of our former patient.

The history of an œdema beginning in the feet and gradually spreading upwards, by itself aroused our suspicion that this was a cardiac œdema. As we shall see later, the œdema would have indicated a totally different origin had it at once affected the body more generally, as when we observe, for example, a swelling of the eye-lids and a puffiness of the face going with an œdema involving all the tissues of the body, as in the so-called parenchymatous

nephritis. It has long been known that an œdema of the feet is most likely to be the first sign of a cardiac œdema because the distance of the feet from the heart and the maintenance of an upright position aid in aggravating the lack of circulation to the extremities induced by the weakness of the heart itself. By doing away with the upright position we are likely to see such patients improve very quickly, in other words, with no methods of treatment other than bed rest.

At other times we seek aid from the administration of digitalis or other cardiac stimulants like strophanthus, caffein, or camphor. I call your attention to the use of these drugs merely to emphasize how absurd are the notions that an increased capillary blood pressure is responsible in the first place for the œdema. Were our current notions of œdema correct, these drugs that raise blood pressure ought to increase œdema, yet they never do. Why these drugs produce their good effects is understood at once if we recall that they act as cardiac and respiratory stimulants, thus favoring the circulation of blood through the œdematous tissues. This means, of course, a better oxygen supply to the tissues and a better removal of the carbonic acid and other acids formed in them, with consequent reduction in the capacity of the tissues to hold water and therefore a reduction in the œdema of the suffering tissues.

Let us follow, for a moment, the future of the patient with heart disease in whom bed rest, drugs of various sorts, etc., are powerless to stay the progress of his disease. What are we likely to see? Coincident with or at times following the first swelling of the feet, which gradually spreads upwards, we are likely to observe not only a certain degree of dyspnea, but also evidences of an œdema of the tissues lying nearer the heart. The liver and kidney may become involved, both of them becoming swelled, because of a so-called passive congestion. We reserve a discussion of the changes in the kidney until later, for they furnish the stepping stone to the orthodox nephritides which are to constitute the main point of discussion for this evening.

§ 4

How are we to understand the mechanism by which the liver œdema so common in these cardiac cases is brought about? It is usually held that there is a backing of blood into the liver and that

the increased capillary blood pressure resulting therefrom forces blood into the liver cells. When we try to produce an œdema of the liver by experimental means, we find that none results from ligation of the portal vein. Failure of the portal blood to go through the liver is, therefore, not a cause of œdema in this organ. This fact does not surprise us. The portal blood, highly venous, has nothing to do with the maintenance of the liver parenchyma in its normal state. We have an œdema of the liver, however, when the hepatic vein is tied. As you know, the mixed blood from the portal circuit and the arterial blood entering the liver through the hepatic artery leaves the liver through the hepatic vein. The parenchyma of the liver is supplied with oxygen through the hepatic artery, so it is not surprising that the most effective way of producing an œdema of the liver is through ligation of this vessel. This deprives the liver of oxygen; and an abnormal accumulation here of carbonic and other acids follows. Ligation of the hepatic vein brings about the same general effect by indirect means and when heart disease leads to an œdema of the liver, it is to be understood similarly. Blood backed into the hepatic circuit dams the influx of arterial blood through the hepatic artery, the whole state being aided and abetted, in many instances, by an improper activity of the heart muscle and heart valves in propelling the blood forward, so that an adequately arterialized blood stream really never gets into and through the liver.

§ 5

As the cardiac patient fails further, he may begin to show signs of œdema in the upper portions of his body, as in his upper extremities, and his face and neck. At this stage, he will probably complain of headache and appear drowsy, and coincident herewith, or, at times, preceding it, there may be a persistent nausea, associated perhaps with vomiting. While such nausea and vomiting are commonly, and, no doubt, with some justice, ascribed to a passive congestion and œdema of the stomach, I should like to emphasize that quite as important a factor is that of acid intoxication of the central nervous system. Nausea and vomiting are common expressions of an acid intoxication with œdema of the medulla. I cannot press this home to you too strongly, because its importance is ordinarily overlooked. These signs represent

to me the earliest indication of what will shortly be a serious pathological condition. The headache with drowsiness and the gradually increasing stupor are similarly to be taken as evidences of an acid intoxication and œdema of the brain; wherefore, these inadequately appreciated signs and symptoms are also to be ranked among the important first danger signals informing us of the existence of a serious state in the brain. If something is not or cannot be done to relieve such brain and medullary œdemas, the headache and drowsiness give way to stupor and coma, while the increasing medullary involvement is expressed in the heavy and stertorous breathing or CHEYNE-STOKES breathing so frequent before death.

§ 6

If the patient does not die at this time we may find, on examination, that the alveoli of the lungs are beginning to show evidences of fluid in them and that the bronchi are gradually filling; the patient is developing a pulmonary œdema. It is often said that a pulmonary œdema is the cause of death in these cardiac patients, but as JULIUS COHNHEIM pointed out, many years ago, "Patients do not die of pulmonary œdema, they develop a pulmonary œdema because they are dying." The reasons for the terminal "pulmonary œdema" are the same as those discussed in the case of the liver. Ligation of large trunks of the pulmonary artery is not followed by pulmonary œdema, nor is even the ligation of large branches of the pulmonary vein, the reasons being that the pulmonary circuit does not feed the parenchyma of the lung. The arterial blood supply to this comes through branches of the aorta, namely, the bronchial arteries. Because these lie so near the heart, the lung will continue to be supplied with arterial blood of such quality as may be available almost until the end, and hence it is nearly the last to be involved in the œdematous process. Last of all to be shut off from the arterialized stream will be the heart itself, for by the coronary arteries, blood will be carried through the heart muscle until the final stroke of the pump.

§ 7

Let us go back now to a consideration of the changes that occur in the kidney in cases of heart disease. By a mechanism similar

to that active in the other tissues of the body, the kidney, too, develops an œdema. Through the passive congestion an inadequate blood flow through the kidney is established, on account of which this organ also begins to suffer from an accumulation of carbonic acid and of other acids in it. These acids, by enabling the protein colloids of the kidney to hold a more than normal amount of water, lead to a swelling, and thus the increase in the size of the kidney, so common in heart disease, is accounted for. But at the same time that this is happening to one group of the colloids of the kidney a second group is being precipitated, leading to the appearance of granules in the kidney cells. These granules give the tissues a cloudy or boiled appearance, which, together with the swelling of the other group of colloids, yields the combination known as "cloudy swelling." Under the influence of the acids, the kidney proteins also tend to go into solution and this marks the origin of the albumin we find in the urine. Such albumin in the urine as is not due to gross breaks in the blood vessels, or to an escape of the formed elements of the blood by diapedesis, is due to a "solution" of the kidney. Moreover, under the solvent action of the acid, the kidney structures tend to fall apart. Since the colloid material attaching the kidney cells to their base is more readily soluble in acid than the kidney cells themselves, the cells stick together and separate in groups from their tubules. This marks the origin of the kidney casts. Whether these shall be epithelial in character, granular, or hyaline, depends entirely upon the concentration of acid present in the kidney, the concentration of the various salts, and the length of time they have together acted upon the kidney structures. But under the influence of an acid the power of the kidney to give off water, in other words, to secrete urine, is also impaired; consequently a decrease in urinary output goes with the uncompensated heart lesion.

The fact is not strange, therefore, that casts, albumin and a decreased water output are the almost constant accompaniments of every uncompensated heart lesion. Obviously the intoxication of the kidney with acids (and similarly acting substances) must increase, other things being equal, with increasing failure of the heart, and so we are not surprised to find that less and less urine is secreted, containing more and more albumin and casts, as the heart impairment grows. On the other hand, we are all familiar with the often rapid clearing of the urinary findings when

acute attacks of cardiac failure respond favorably to bed rest, cardiac stimulants, etc.

The presence of an increasd amount of acid in the kidney in all these uncompensated heart cases is proved not only by the direct finding of more acid in the blood of these patients, but by an analysis of the urine. It is a familiar fact that the acidity of the urine in cardiac patients, whether measured by titration or in the more popular modern terms of hydrogen ion acidity, always shows an increase above the normal.

§ 8

Let me call your attention to an easy and rapid clinical method of measuring approximately the hydrogen ion acidity of the urine. While such a test alone does not permit us to make any absolute generalization regarding the state of the patient or his future, it nevertheless gives us some valuable points regarding treatment and prognosis. I would suggest that, instead of using litmus in testing the reaction of the urine, you use a saturated alcoholic solution of methyl red. This indicator is less sensitive to acids than is litmus. In using it, two drops of the solution are added to five cubic centimeters of urine. The container should be, preferably, a porcelain dish, or a beaker set upon a white background, and previously cleaned in distilled water, or, if this is not accessible, first rinsed in the urine to be tested. We have found by clinical study that normal individuals at bed rest and on a full diet do not run a urine acid to methyl red, except perhaps in the early morning hours. On the other hand, cardiac cases and many others pass urine acid to this indicator straight through the twenty-four hours.

Let me say to you that it is an acid intoxication which in the cardiac case ultimately kills the patient. It is, therefore, of much moment to discover its existence, its intensity and its persistence. It has been our experience that no patient recovers, be he a cardiac case or any other type, who secretes urine that remains persistently acid to methyl red.

On the other hand, a fall in acidity to below the turning point of methyl red, whether accomplished through bed rest and the unaided efforts of the patient in overcoming his pathological state, or aided, on our part, by an active administration of alkali, means

an improvement in our patient and a correspondingly more hopeful prognosis.

A careful following of the acidity of the urine constitutes our only correct guide to the amount of alkali that must be administered. This must be given until the patient shows urine persistently alkaline to methyl red. In normal individuals at bed rest five grams of sodium bicarbonate, for example, will usually suffice to efface the acid reaction of even the morning specimens of urine. Cardiac cases, depending upon their severity, will require 30, 50, or even 100 grams of sodium bicarbonate in twenty-four hours before this result is obtained. I have given even larger amounts than this by mouth, rectum or intravenously, and not changed the hydrogen ion acidity of the urine. In my experience, such cases die. When death will take place cannot, of course, be stated in absolute terms. It may occur in a few hours, or a few days; and I have never seen such patients live beyond three or four weeks, when it has proved thus impossible to reduce the acidity of the urine by appropriate means.

§ 9

The œdematous patient with heart disease that I have just showed you really represents, therefore, one suffering from a general intoxication. While he is primarily a sufferer from heart disease, he is, physiologically considered, really suffering from a general intoxication with carbonic, lactic and other acids. This acid intoxication is responsible for his general œdema including that of his kidneys; it is primarily responsible for all the changes which these organs show, and which, were we unconscious of their cardiac origin, we would be willing to call "nephritic." As a matter of fact, we might as well call them such, for this will serve to bring them, as it should, into close union with those similar urinary findings which most people are willing to concede as truly nephritic, but for the origin of which other factors are responsible. I can make this matter clear to you by showing you the next patient. We shall find that she, too, has been the victim of a general intoxication with sub-oxidation acids and like substances, but the mechanism by which the sub-oxidation acids were produced in her instance was not cardiac in type—she was the victim of a poisoning of the exact nature of which we know as yet little or nothing.

3. The Nephritis of General Intoxication

§ 1

In a patient with heart disease, an abnormal production and accumulation of acids and like substances in the tissues of the body is brought about chiefly through the inadequate supply of oxygen that is furnished to the tissues. Obviously, the same sort of intoxication would have to follow were we, with maintenance of a normal circulation and plenty of oxygen reaching the tissues, so to damage the cells themselves with a poison of some sort that they could not use properly the oxygen after it had reached them. We would then again have various abnormal sub-oxidation products accumulating in the affected cells, and the result would be an œdema of the involved tissues which, depending upon the organ involved and its intensity, might be of little or much significance; and depending upon the nature of the intoxication and its persistence, constitute an evanescent or death-dealing affection. The patient that I now show you is no longer ill, but she has just come through such an intoxication as I have outlined.

§ 2

Mrs. R. is thirty years old. She entered the hospital about six weeks ago, when practically at term, not because she was suffering from any symptoms, nor because her attending physician, Dr. W. W. Wymore, had noted anything abnormal about her, but because she felt the hospital a better place than home in which to be delivered. Repeated urinary examinations in the hospital were negative. The record shows that she voided a good quantity, namely, from 270 to 330 cc. (9 to 11 ounces), at a time, several times in each twenty-four hours. Her general physical state continued good. She went into labor early on Sunday morning, July 25, and toward daybreak was delivered of a normal living girl. The labor was not particularly hard; a little ether was used during the delivery of the head. Nothing abnormal was noticed until after delivery. Her temperature throughout her stay in the hospital had not risen above 98.8° F., nor her pulse above 66.

For several hours after delivery everything continued well; then, waking from a period of somewhat broken sleep, she complained of severe headache. Please note this symptom, the

only one she had; the tremendous importance of it is not generally recognized by our medical men. Its significance we shall discuss later.

Her urinary output diminished somewhat after delivery and a catheterized specimen showed it to be acid to methyl red and para-nitrophenol. At this time some albumin and casts were found. There was also apparent about the face a slight puffiness, and a very mild grade of œdema could be noticed in the skin generally. This general state continued until some twenty-four hours after her first labor pains, when she began to vomit. She seemed also more than usually drowsy. Several teaspoonfuls of sodium bicarbonate and two teaspoonfuls of saturated magnesium sulphate solution by mouth were ordered and the patient was left to herself. Her headache and vomiting persisted. Several hours later she had a convulsion.

§ 3

Let us stop at this point and try to picture what had happened to this woman. If she had had casts and albumin in her urine before delivery (or, as many would say, since she had casts and albumin in her urine after delivery) this patient would have been alleged to have been an example of a so-called pregnancy nephritis with "uremic" symptoms. But there is something illogical in the view that such a patient is suffering from a retention of various poisonous substances which should have been eliminated through the kidney and hence is uremic, when she shows absolutely nothing in her urine that would indicate any disturbance in the kidney function. Yet this view continues uncombated throughout the world. But not only does the history of this patient prove conclusively the absurdity of a belief which would maintain that such symptoms as this woman showed are secondary to a loss of kidney function, but animal experiments prove it. Were those signs and symptoms which clinically we are in the habit of designating as uremic really secondary to a loss of kidney function, then we should be able to reproduce this picture experimentally through double nephrectomy in animals. But when we remove both kidneys from an animal, or, when surgeons by mistake remove an only kidney, the victims of these procedures show none of the signs and symptoms generally classed as uremic, although

they live many days. Even when in isolated instances they live two or three weeks after such accidents, they remain perfectly clear mentally. Neither do these patients thus deprived of their kidney function develop an œdema.

Let us compare with these results those of another set of experiments. Let us give some animals one of the generally acknowledged and popular "kidney poisons" like uranium nitrate. Within a few hours after the poison is administered the animals begin to develop a generalized œdema, amounting in the case of frogs to an increase in body weight of 25 to 50 per cent in one or two days. These animals also show a decrease in urinary output, with casts and albumin. They are, in other words, nephritic. But they are likely to be drowsy also and sometimes, on irritation, they will suffer a convulsion. While after double nephrectomy animals may live many days, these poisoned ones rarely live more than five or six. How are these differences to be understood? It is generally held that in the poisoned animals the œdema, stupor, etc., are secondary to a loss of kidney function, but, as you observe, this interpretation cannot be correct.

The animals poisoned with uranium nitrate present the same picture that this woman did when, several weeks ago, she was suffering from an intoxication incident to her pregnancy. In both instances the whole organism is the subject of a general intoxication. As it strikes the kidneys, the intoxication produces an œdema of these organs, with the appearance of albumin and casts; as it affects the subcutaneous tissues, an œdema results here; and as it affects the brain and the medulla, these organs swell, thus giving rise to the headache, the nausea, the vomiting, and ultimately the stupor, coma, convulsions and death, which so frequently close the scene. They are the victims not of an uremia, but of an acute toxic œdema of the central nervous system, and this is not secondary to an imagined loss of kidney function—in the case of this patient, as you will remember, there were at first no kidney signs whatsoever—but due to the direct action of the toxic agent upon the central nervous system itself. The brain effect is not secondary to the kidney disturbance, but both are due to the same cause.

I cannot emphasize too strongly the importance of getting this relationship clearly in your minds. How often are we stopped by one of our colleagues who informs us that some patient, to his

great surprise, has just died in coma and convulsions, when, as in this patient, the urinary findings were trifling in nature, or entirely normal. So long as we make the head symptoms secondary to the kidney findings, this mistaken feeling of security will go on. But when once we recognize that the head symptoms and the kidney findings represent pathological processes of the same type—essentially œdemas—and that the one is not consequent upon the other, but that both are due to the same toxic agent acting simultaneously upon different organs, a better understanding of our clinical problem will result.

A poison injected into an animal or produced in a human being, need not, of course, involve all organs equally or at the same rate, and so it happens that in these pregnancy intoxications we may find the signs from the kidney predominating at one time, at another those from the head. More rarely the liver is chiefly involved, and then we speak of an "acute yellow atrophy," a "chloroform," or "ether liver," or something of that sort, indicating that the liver has been the chief sufferer in the general intoxication. I have seen pregnancy patients with suppression of urine lasting days, but the brain completely clear, and I have also seen convulsive seizures in women who showed no abnormal urinary findings whatsoever. These things mean that in the former instance, the kidneys were more acutely poisoned than the head, while in the latter it was the brain that suffered the more severely.

This is the reason for the importance of headache or nausea, drowsiness or vomiting in pregnant women. These cause me more anxiety than complete suppressions of urine, for they represent, in essence, symptoms of a dangerous degree of brain swelling, and therefore betray a condition which portends greater immediate danger, and which is combated with greater difficulty than a complete suppression of the kidney function.

§ 4

The patient before us had, at the end of her first eighteen hours after delivery, little evidence of a kidney or general tissue involvement. Her first symptoms and signs pointed to an œdema of the brain, and it was toward this, more specifically, that first attention was directed. Beginning with headache, she developed

nausea and vomiting, following which there came stupor and a convulsion.

Please remember that these signs began *after* delivery. I have heard more than one of my critics say that the good results which follow such treatment as was given this patient are but accidental, and that even without such treatment these patients, after delivery, "take their natural course." I regret deeply that this "natural course" is not usually along the road toward life, but more commonly toward the great beyond. It is a fact little remembered that one-third, and according to some authors, one-half of all the convulsive seizures incident to pregnancy do not develop until after delivery. That is what happened in this patient. The reasons are to my mind perfectly clear. Before delivery these patients usually show a high degree of acid intoxication, although it may not have reached the point of producing an œdema of the kidney, of the head, or of some other organ. But to the initially high acid content, add the element of acid production incident to the muscular efforts of labor, or that of the acid intoxication consequent upon narcosis (whether by chloroform, ether, morphin or scopolamin), and the sum of the two is sufficient to push many a woman who has just managed to drag herself through her pregnancy, over the line. So in this patient head symptoms first appeared *after* the fatigue of delivery, as did the albumin and casts.

§ 5

The administration of sodium bicarbonate and of magnesium sulphate in several small doses represented a first attempt to meet the œdema of her brain, that of the kidneys as expressed in her urine, and that of her tissues generally, as observed in her slight general œdema. This mild scheme of therapy permitted her to hold her own with decrease in the intensity of her various symptoms and signs for about three days, when her headache again became very severe, her nausea and vomiting reappeared, her drowsiness rapidly increased, and another convulsion took place. The patient then went into a coma from which she could not be roused. While in this state, a series of major and minor convulsions occurred.

Very clearly we had not been sufficiently aggressive in our

dehydration therapy. Urine obtained by catheterization at this time proved acid to methyl red and para-nitrophenol, and was filled with albumin and casts. In other words, in spite of the steady administration of alkali, we had given not nearly enough.

§ 6

As you know, two elements are of much importance in determining the amount of water that a simple protein or a tissue holds. When fibrin, for example, is put into water it swells somewhat, but if put into acid it swells very much more. Neutralization of the acid with an alkali reduces the swelling. But even without neutralization of the acid we can decrease the swelling by adding various salts to the acid. The amount of reduction thus produced is determined by the concentration of the salts, the dehydration increasing with every increase in the concentration of the added salt.

In order to dehydrate our patient more effectively, more particularly in order to dehydrate her brain, we decided upon the administration of alkali and sodium chlorid intravenously. A mixture that may be safely used and which contains both alkali and a readily diffusible salt in sufficient concentration to bring about a dehydration of œdematous tissues, has the following composition:

Sodium carbonate "dried"	8.4	grams.
Sodium chlorid	28	grams.
Distilled water, enough to make	2000	cc.

We gave 1800 cc. of this mixture through a vein in the bend of the elbow, taking some fifty minutes to make the injection.

Our patient had no more convulsions after this first injection. It became possible to rouse her slightly and a perceptible increase in her urinary output took place, with a fall in acidity to below methyl red. The patient continued in this state until the evening, when, because she had not yet cleared mentally, we decided that more dehydration of the brain was necessary. What to do in our continued efforts in this direction had next to be considered. We might have repeated the alkali-salt mixture first used, but for reasons that I shall try to make clear, we decided that an intravenous injection of magnesium sulphate was better. Generally speaking, the greatest dehydration of the body colloids that can

be produced is obtained when they are kept in a neutral medium of high salt content, and it is this state that we should try to induce. An index to the attainment of a neutral state in the body, as when alkalies are being administered, is furnished by an examination of such different secretions from the body as urine, saliva, and sweat. We should attempt to get and maintain these persistently neutral to litmus. Even when this point has been reached and held for a short time it is, of course, still possible for local organs to be harboring more acid than normal; but if the secretions from the body are kept persistently neutral, or, for a time, even slightly alkaline, it is reasonable to suppose that all the tissues of the body must ultimately also attain this reaction.

By injecting alkali intravenously, we had succeeded in causing the originally high acidity of the urine to fall somewhat; and by administration of alkaline waters fortified with sodium bicarbonate and magnesium oxid, we succeeded in holding our patient neutral. We were, therefore, evidently giving her the best possible chances, from this point of view, of recovering from her brain œdema. But as she did not clear as rapidly as we could wish, in other words, did not wake up thoroughly, we knew that more brain dehydration was imperative and so looked about for additional help.

§ 7

The dehydration of a protein outside of the body by salts depends not only, as I have already indicated, upon the concentration of salt used, but also upon the kind of salt. Certain salts are far more powerful in this regard than others. Calcium, for instance, is a more powerful dehydrant than magnesium, and magnesium is more powerful than sodium. On the other hand, a sulphate is more powerful than an acetate, iodid or bromid, and these in turn act more strongly than a chlorid.

In the first intravenous injection, sodium chlorid in a more than "physiological" concentration was used to accomplish the dehydration of the brain. Not finding it as effective as we could have wished and satisfied on the whole with the degree of alkalinization that had been accomplished, we turned to the use of a salt which would act more strongly than the sodium chlorid. Since experimental study has shown magnesium sulphate to be, roughly speaking, about sixty times as powerful a dehydrant, molecule

for molecule, as sodium chlorid, we decided to use this material intravenously.

This salt may be used safely in the form of a sterile 2 per cent, or $2\frac{1}{2}$ per cent solution, and in amounts up to 8 grams of the salt. Ordinarily 200 cc. of such solutions constitute the ideal amount for a first dose. If this alone does not yield the desired effects, the dose may be repeated. This is better than giving a single large dose once. The injection must, moreover, be made slowly. After injection into the blood, the salt diffuses into the tissues and dehydrates them. As water is freed from the tissues, it pours into the blood stream, which is thereby increased in volume. This brings about an increase in blood pressure, which is maintained until the liberated water is lost from the body through one of the secretions, as the urine or sweat. In order not to overwhelm the circulation with too large an influx of water at one time, *slow* injection, in other words, careful dehydration of the body tissues, must be insisted upon.

It was after an injection of 250 cc. of a 2 per cent magnesium sulphate solution that our patient woke up completely. When she became conscious we questioned her regarding herself, and, with due care not to suggest the answers we might like to hear, we asked about her headache, her nausea, and her vomiting. For a number of hours after the injection of the magnesium sulphate these symptoms were absent, and we contented ourselves by trying to hold what we had won through administration of alkali and magnesium sulphate by mouth. But some twelve hours after the magnesium sulphate injection, she again became drowsy, and complained of headache and nausea. This was an indication to us that her brain swelling was again increasing, so a second dose of magnesium sulphate was given as before. Full consciousness returned, and her nausea and vomiting disappeared. As she awoke, however, she showed a mental disturbance, which the psychiatrists would have diagnosed as a mild mania. She talked excitedly in answer to our questions, did not know where she was, did not recognize the members of her family, and was otherwise confused in mind. This mental disturbance continued about five days. Since we regarded it as but another expression of her central œdema, we kept on during this time with sufficient alkali by mouth to keep her urine persistently neutral, and with enough saturated solution of magnesium sulphate in small doses to yield

two or three easy evacuations of the bowels in each twenty-four hours. The primary purpose in giving magnesium sulphate was not the catharsis, but absorption of the salt and the maintenance of a steady tissue dehydration. During the five days that such therapy was continued, the general œdema disappeared from the body and the albumin and casts steadily diminished. By the second day the urine was almost clear and by the third it was entirely so.

§ 8

I cannot help commenting upon the mental state of this patient. It seems so obvious that the purely puerperal manias are only toxic œdemas of the brain, that I cannot help wondering whether much could not be done for many of the manias due to other causes, which fill our insane asylums, if they, too, were treated on the assumption that they are suffering from cerebral œdemas. Autopsy findings in many instances show nothing more. In our eclampsias, a general toxic cause of unknown origin is responsible for the mental disturbance, and similar intoxication seems to underlie at least some of our orthodox psychiatric cases. Or such brain œdemas with their resultant abnormal mental states, as seen in our insane asylums, might be due to direct infections of the brain, or to disturbances in circulation as produced by arteriosclerosis, the whole set of changes being the same in result but different in their origins, as when similar changes affect the kidney or some other organ. While the possible fruits of treatment and the prognosis would depend upon the nature and the persistance of the causes leading to the cerebral œdemas, much could to my mind be done to relieve at least some of these patients if they were made the subjects of an adequate dehydration therapy. My own opportunities to test out these ideas have been rather limited, and probably must continue to be; but it is a study which some of our psychiatric colleagues could undertake without harm to their patients and possibly with much good.

§ 9

Every effort was made throughout this patient's illness to feed her, no restriction being placed upon the character of her food. Milk and eggnogs (without whisky) were given every three

hours in as large quantities as she could be made to swallow, while orange juice, grape fruit, mushes and gruels, all well sugared, were pushed to the utmost. It is most important that all these patients have plenty of food, and that special care be taken to administer enough carbohydrate. There is no objection to allowing proteins; I give them as soon as the patient will swallow them and of a kind that appeals to the appetite of the individual. It is absurd to think that the proteins of milk, of eggs, or of white chicken are any better than the proteins of beef, of mutton, or lamb (since before absorption they are all broken into the same forty amino-acids), and so I make every effort to take these patients off their nearly always inadequate "light" and "slop" diets so popular in our hospitals, and to give them good mixed rations of bread, toast, potatoes, rice, vegetables, steaks, chops and fish. On such a regimen this patient cleared completely in less than a week, and after about ten days spent in convalescence, she left the hospital in as good a general condition as most women show after a normal pregnancy.

§ 10

To the use of alkali, of hypertonic sodium chlorid and of magnesium sulphate, it is frequently well or imperative to add glucose (dextrose). Because of inadequate feeding, because of the vomiting of such food as has been taken, and for certain other reasons, pregnant women frequently suffer from carbohydrate starvation, so that they become the victims of a deranged body chemistry quite similar to that of diabetics. In other words, their tissues produce large quantities of the acetone bodies (acetone, diacetic acid, beta-hydroxybutyric acid). If something is not done to stop the formation of these substances or to neutralize their toxic effects (as by the administration of alkali), the patients add the acid intoxication from these sources to any other acid intoxication from which they may be suffering. In all pregnant women, whether nephritic or not, it is therefore important to discover if evidences of such a carbohydrate starvation are at hand.

Without resorting to the more refined methods for determining qualitatively and quantitatively the "acidosis" compounds present in the urine, it is certainly an easy matter to do the ordinary tests for diacetic acid, or acetone. It is a safe error to regard every patient showing a persistent ferric chlorid reaction in the urine, for

example, as suffering from carbohydrate starvation and to make special efforts in all such patients to supply the deficit in carbohydrate intake. When such deficit is noted in a pregnant woman who is in coma or convulsions, or is showing an alarming lack in urinary output, the twin necessities of feeding carbohydrate and of producing a dehydration of some one or all the tissues of the patient may be well satisfied by giving concentrated glucose (dextrose) solution intravenously. Sterile 45 per cent solutions in amounts from 100 to 200 cc. at a dose do very well. These injections, too, must be given slowly, and it is better, for the reasons already discussed, to give several smaller injections than a single large one. Since the body uses up several hundred grams of carbohydrate (400 to 500) in each twenty-four hours, an overdose of glucose can hardly be given. Such intravenous injections serve the purpose of furnishing food, while they produce at the same time the necessary dehydration.[1]

§ 11

A word must be said regarding the administration of water to these patients. When we are actively engaged in trying to dehydrate the body tissues by any scheme whatsoever, it is obviously wrong to administer water by mouth or otherwise, for dehydration depends upon the establishment in the tissues of an increased concentration of alkali or salt or sugar. No water should, therefore, be given for two or three hours following our attempts at dehydration. But once the dehydration has been accomplished and physiological conditions in the involved organs have been at least partially re-established, then, if we desire more urine than is being put out, or more of some other secretion from the body, we can accomplish this only by furnishing the secreting glands free

[1] R. T. Woodyatt (Jour. Amer. Med. Assoc., **65**, 2067 (1915)) has devised an injection apparatus which will give accurately and at any concentration, any amount of glucose that we may wish to give a patient, and for any length of time. No further injury need be done the patient than is incident to the insertion of a hypodermic needle into a vein. Aside from its immediately practical value, Woodyatt's work is of fundamental biochemical and clinical interest as it establishes accurately for the first time, the toleration limits of various sugars. For dextrose this limit is 0.85 gram per kilo per hour, above which come into play its dehydration effects upon the tissues with the resulting rise in the various secretions, more particularly the urinary secretion (diuresis).

water. Obviously, therefore, judgment is required to know when to withhold water and when to press it, the matter being governed by the relative importance of the effects we wish to obtain—in other words, whether in the given clinical case the dehydration of a certain organ is the vital consideration, or whether the furnishing of free water to an active gland is the end sought.

§ 12

What is the prognosis so far as the kidney is concerned in one of these pregnancy nephritides? If these patients do not die in their eclampsias and we succeed in clearing the urine of pathological findings, the prognosis is entirely good. These patients do not go on to a chronic nephritis, nor do they retain any increased tendency toward it. They are not more than commonly liable to renewed albuminuria, to uremia and other things of this type, as is so generally taught. Once over their pregnancy and cleared of the pathological findings incident thereto, they are as good as before. The termination of pregnancy means a termination of their intoxication, and if we have succeeded in protecting them from the consequences of this they have recovered permanently.

We should always be suspicious of the nephritis that continues after delivery and in which a proper attempt has been made to clear the urine with alkali, salt and adequate feeding. The nephritis is then almost certainly not purely of pregnancy origin but has other causes also. The more usual possibilities are that the kidney is the seat of an infection, or that it is the victim of vascular (arteriosclerotic) change. Just because a woman happens to be pregnant, a nephritis which she may show must not at once be attributed to the pregnancy. Pregnant women may become nephritic from any of the causes that may strike you or me. An infection of the kidney, or the consequences of arterial disease, may come to light for the first time in a pregnant woman quite as easily as in anyone else. This possibility of causes other than the pregnancy for these kidney changes needs, therefore, always to be borne in mind in determining the meaning and prognostic importance of the casts, albumin, etc., found in the urine of a patient, before, during, or after pregnancy.

§ 13

When once it is recognized that a pregnancy intoxication represents a general one affecting all the body cells, but which may make certain organs, like the kidney or brain, the chief sufferers and so have these dominate the general picture, the relation between this type of patient and that of all other patients suffering from a general intoxication is seen to be very close. The commonest clinical types of such other general intoxications are those incident to the anesthesias with chloroform, ether or nitrous oxid, and those secondary to heavy doses of alcohol. But this general type of intoxication is also characteristic of the action of the various metals, as lead, uranium, tin, zinc, mercury and arsenic (or its various derivatives like salvarsan, neo-salvarsan, etc.). The clinical picture of poisoning with any of these is much the same, and they all simulate clinically a pregnancy intoxication. There is a tendency toward a general œdema, toward stupor, coma and convulsions; or, when the kidney is involved, casts and albumin with a decrease in urinary output. But just as in the patient I have been showing you, none of these things is secondary to some other—the head symptoms are not secondary to the kidney signs, for instance—but all are equally due to the primary intoxication which tends to attack all the cells of the body at the same time.

§ 14

It is clear that when a nephritis develops in consequence of some soluble poison passing through the kidney, as occurs in any of the general intoxications, the poison must tend to involve the whole kidney at once and more or less equally. The same thing is true, of course, if in consequence of a circulatory disturbance the whole kidney is at once made the subject of a state of lack of oxygen. In all such cases, therefore, the whole kidney becomes swollen and grayish, the secretion of urine drops to little or nothing and such urine as comes is heavily charged with albumin and casts. Conversely, a decrease in the urinary output, much albumin and many casts, are generally to be regarded as signs indicating that the whole kidney is involved. These things should be borne in mind, for they help us to interpret properly our clinical pictures.

You will observe that the signs and symptoms I have detailed

constitute the group generally held to be characteristic of (generalized) parenchymatous nephritis. Our older clinical teachers used to tell us that this type of nephritis was commonly associated with a generalized œdema, the first evidence of which was likely to show itself in a puffiness about the eyes. After what has been said, this generalized œdema is evidently not be to regarded either as characteristic of, or secondary to the parenchymatous nephritis. It only shows that the patient as a whole is the subject of a general intoxication. Since the toxic agent may attack and produce an œdema anywhere in the body, it does not surprise us that the eyelids should be particularly liable to present the first evidences of disturbance, for these tissues have a particularly great capacity for absorbing water.

4. Spotty Parenchymatous Nephritis Due to Infection of the Kidney (Infectious Nephritis)

§ 1

The kidney may evidently become the victim of a pathological process which does not destroy the whole kidney uniformly and at once, but affects only pieces thereof. Thus, micro-organisms may be sown into the kidney, and according to their lodgment may give rise to areas of local intoxication and death. But between the spots thus affected (which show the same series of changes that we observed before in the whole kidney, in other words, those of a *spotty* parenchymatous nephritis), we have entirely normal kidney substance. Let me call your attention to the fact that when we reduce the kidney substance in animals to one-fourth of the total amount, or even less, by removing first one-half or more of one kidney and later the whole of the opposite kidney, these animals show no decrease in urinary output, no casts or albumin, nor anything else to indicate that they are not entirely normal. Functional tests, be these water tests, or dye tests, or what not, all yield entirely normal findings in such animals. In other words, so far as kidney function is concerned we do not seem to suffer from any lack of it as long as one-fourth of the kidney substance is preserved intact. Or, to turn the matter about, our present tests yield no evidences of impaired kidney efficiency until more than three-

fourths of the normal total of kidney tissue or of its functional capacity is destroyed.

These facts are of importance, you observe, because they explain why patients with a spotty parenchymatous nephritis, whatever its origin, do not show a decreased urinary output or a decreased elimination of any such substances as come out normally in the urine, or a decreased elimination of such as are introduced from without to indicate degree of function even though goodly portions of their kidney are in a state of active destruction.

I have no patient here to illustrate this infectious type of spotty parenchymatous nephritis, but to fill in the gap let me read the history of one such case.

§ 2

Miss H., aged forty-one years, and a teacher by occupation, gives a family history which does not interest us. For four years she has not been able to do her work because constantly below par physically. She has occasionally been the victim of "stomach trouble," characterized by a sensation of pain in one spot in the stomach shortly after eating. There have, however, been no recent attacks of this type. During one such attack she vomited red blood and at another time she observed that her stools were very black. About two years ago, albumin and casts were found in the urine and have been present constantly since.

Physical examination of the patient reveals rather prominent eyeballs with a lagging of the upper lids, but no tremor and no increased heart rate. The thyroid gland is perceptibly enlarged; physical examination of her heart and lungs is negative. Some tenderness on pressure can be elicited in the midline below the tip of the xyphoid process. There is no tenderness in the abdomen elsewhere. The legs are negative. The sockets of several teeth are infected and the gums about them, red and swollen. The tonsils are large and red, showing crypts filled with caseous material. The lymphatic glands of the neck on both sides of the sterno-cleido-mastoid muscle are readily palpable. The systolic blood pressure is 125 mm. of mercury, the diastolic, 88. In each twenty-four hours, 1500 to 3000 cc. of urine are voided, depending upon the amount of fluid administered. When in bed, the patient shows only occasional specimens of urine acid to methyl red.

Six to eight grams of albumin are found in the liter. Microscopic examination of the urine shows relatively few casts, but large numbers of white blood cells.

On the basis of these findings, a diagnosis was made of chronic tonsillitis and chronic alveolitis with metastatic infections of the thyroid (chronic thyroiditis), the stomach (chronic gastric ulcer) and the kidney (infectious nephritis).

The patient consented to the removal of her tonsils and those teeth most badly infected. With only this, and a scheme of out-of-doors' living, plenty of mixed food, and the administration of enough sodium bicarbonate and magnesium oxid daily to keep her urine constantly neutral to litmus, she has improved steadily during the past two months so that at present she feels in better general health than for years, while a mere trace of albumin remains, and casts can be found in her urine only after long search.

§ 3

This patient illustrates a common type, and one frequently diagnosed as "chronic BRIGHT's disease" or something of the sort, with a gloomy prognosis attached. Experience seems to indicate that such despair is hardly justified, especially if the patient will agree, as did this one, to a thorough cleaning up of those neglected foci of infection which keep seeding the blood stream with bacteria, and so producing new infections as soon as older ones have been overcome.

The diagnosis and proper classification of this type of infected kidney depend upon the recognition of points of infection from which the kidney condition may have arisen, upon the absence of changes in blood pressure, the absence of cardiac hypertrophy and the discovery in the urine of more than the occasional leucocytes that may be found in any acute toxic nephritis. The fact that the urinary secretion per twenty-four hours is normal and may readily be increased through the administration of water is evidence that the whole kidney is not involved, or conversely expressed, the kidney involvement is spotty in type. The urine only occasionally running acid to methyl red, and the albuminuria continuing, even after the mixed urine is kept steadily neutral to litmus, are further evidence in this direction. Spots in the kidney may, in other words, be dying of a local intoxication with acid

(and like substances) without this acid being sufficient in amount to make the whole urine (in other words, that coming from both the diseased and the well portions of the kidney) acid to methyl red.

§ 4

As in this patient whose history I read to you, the prognosis is remarkably good in all of these patients if we succeed in freeing them from their original foci of infection, and then by hygienic methods aid them to overcome the kidney state. Patience is, however, necessary to attain these ends. The kidney findings have not, in my experience, proved apt to clear quickly. At the best, weeks or months may be required, while others only gradually reduce their albumin output from several grams per liter to a trace, discoverable occasionally, in the course of years.

While it is common, even without treatment, to see these patients with infected kidneys improve, they may also, of course, grow worse. There is always the possibility that the infection will become more general in the kidney, either because an original infection spreads through the kidney, soon to involve the whole organ, or because new infections are repeatedly sown into it. The originally spotty parenchymatous nephritis has then become a generalized parenchymatous one, and as this happens, a drop in urinary output to the point of complete suppression may follow, while the relative and absolute amounts of albumin, casts, etc., increase steadily in such urine as may be secreted. Sometimes such patients also come to show a generalized œdema, but for reasons that I have already tried to make clear, this is not to be interpreted as secondary to the kidney change; it is a toxic œdema due to the absorption of poison from the affected areas in the kidney or from infected foci elsewhere in the body, and to the general toxic effects exerted by these substances upon all the tissues.

5. Spotty Parenchymatous Nephritis Due to Vascular Disease (Chronic Interstitial Nephritis)

A. Ambulatory Type

§ 1

The next patient that I show you is Mrs. E., aged forty-nine years. She came to us some seven weeks ago, with a diagnosis of chronic interstitial nephritis and high blood pressure. Her chief complaint was headache. She had also had attacks of pain over the heart and radiating into the left arm. She informed us that for several years her blood pressure had stood as high as 280 mm. of mercury and that it had never fallen below 210 mm. One of the several physicians who have cared for her once found some albumin and a few casts in the urine several years ago, but repeated examinations since by other men have always proved negative in this regard.

Physical examination on her first visit to the office showed a systolic blood pressure of 275 and a diastolic of 140 mm. of mercury. The lungs and abdomen proved negative. The areas of absolute and relative cardiac dullness were increased in all directions but no murmurs were noted. The arteries were palpably thickened wherever they could be felt. Scattered over the body, particularly noticeable in the legs, were numerous veins with thickened walls. When I first saw the patient she possessed a row of heavily infected loose teeth in the lower jaw and, in the upper jaw, several heavily infected and loose teeth carrying bridges. To-night she shows full upper and lower plates of false teeth.

§ 2

In place of the primary diagnosis of chronic interstitial nephritis, I believe it more correct, for reasons that I shall explain immediately, to make the primary diagnosis in this woman read, generalized vascular disease (arteriosclerosis and varicose veins). Secondary to this, there has developed cardiac hypertrophy; and also secondary to the vascular disease, certain symptoms and signs referable to the head and to the heart and, on a previous occasion, to the kidney.

Why, first of all, do I reject the primary diagnosis of chronic interstitial nephritis? She may have a chronic interstitial nephritis, but it is certainly not an important element in her present condition. To regard it in this patient, or in any similar patient, as of primary importance is not only to be wrong in diagnosis, but what is more important, to go wrong in the matter of treatment. Repeated urinary examinations in this patient, which I have made personally, have remained negative. This seems also to have been the experience of various other physicians who have cared for her. There exists no objective reason, therefore, for our thinking that the kidney element is an important one in this case, and it confuses our entire notion of what is the primary trouble, if in just such instances we go on maintaining what is perfectly untrue, namely, that the cardiac hypertrophy and high blood pressure are secondary to a kidney disease of which we find no evidence, and that the headaches of which this patient complained so bitterly are evidences of a "uremia." Not only do animals, or patients, deprived of their kidney function by sudden or more gradual means, never show any increase in blood pressure, nor a cardiac hypertrophy, nor head symptoms at all identical with those which clinically we are constantly given to designating as uremic, but the picture, which this woman and others like her show, can be more easily and more logically interpreted in a totally different fashion.

The primary thing in this woman is the affection of her blood vessels. In consequence of their thickening, loss in elasticity and "spasm," more work is required of the heart in the unit of time, in other words, greater power to force the blood through the diseased blood vessels. The musculature of the heart meets an increased demand for work in the same way that the musculature of the blacksmith's arm meets it, namely, by hypertrophy, and hence the larger heart in this woman. But with narrowed blood channels, the minimum of blood necessary to meet the physiological demands of any organ can evidently be maintained only as the blood is pumped into the organ at a higher pressure. The cardiac hypertrophy and the high blood pressure are not in themselves, therefore, to be regarded as something evil for these patients. They alone make it possible for the various organs suspended from the circulatory tree to continue their normal functions. As the next case will prove to you, it is not high blood pressure, but

rather the inability to get it that kills so many of these patients alleged to be perishing of chronic interstitial nephritis.

§ 3

What are so generally interpreted as the consequences of chronic interstitial nephritis are really the consequences of the vascular disease affecting different organs. As you know, vascular disease does not affect all the blood vessels of the organism either uniformly or with equal intensity. The pathological changes consequent upon vascular disease may in one patient involve predominantly one organ, while in another a totally different one is chosen; and depending upon which organ, or organs, are chiefly affected, the symptoms and signs in one patient will be totally different from those in another.

In the patient before you, the vascular disease has affected chiefly the circulation to the head and to the heart itself. In consequence of a vascular disease affecting the coronaries and their branches, the heart muscle is periodically deprived of an adequate oxygen supply, which is manifested in the periodic pain seizures (angina pectoris) felt by this patient not only in the heart itself, but in the arm.[1] The same vascular disease, as it has affected the circulation to the brain, is responsible for similar periods of lack of blood here, and hence the periodic brain œdemas that are expressed in the periodic headaches so much complained of.

Had the vascular disease in this patient happened to strike the kidneys, piece after piece of the parenchyma would have become œdematous and died. As these pieces became affected, casts and albumin would have appeared in the urine, the number and amount of which would depend upon the amount of the kidney thus attacked. But as long as one-fourth of the total amount of kidney substance remained unaffected, the urinary output would have been normal, all functional tests would have yielded normal figures, and, so far as the kidneys were concerned, the patient

[1] I am accepting here the commonly given explanation for the pain seizures of angina pectoris. Arthur Dunn emphasizes that physical examination of the heart during an angina attack reveals nothing analogous to the disturbances observed physiologically when the coronary circulation is interrupted. His criticisms may compel a revision of our present views. Dunn holds a periodic stretching of the heart ring or the first portion of the aorta as more probably the etiological factor.

would never have grown conscious of any trouble. Very commonly the kidneys are thus affected in vascular disease and, in consequence of the gradually progressing destruction of piece after piece in the kidney, we get the picture which at autopsy we call chronic interstitial nephritis (small red kidney). But in the patient before you little or none of this particular type of change has occurred.

Recall, for a moment, the high blood pressure which this patient has shown and still shows, and then consider how stupid are our notions when such pressure is attributed to "kidney disease." I have a number of patients in my care now in whom the blood pressure is constantly running above 200 mm. of mercury. Two that I remember at this moment have for years been carrying a blood pressure of 280 and yet they have never had an albuminuria, at any time. I call your attention to these facts to emphasize how we have gotten cause and effect turned about. It is not the kidney disease that leads to the high blood pressure, cardiac hypertrophy, etc., but it is the vascular disease which, when it happens to affect the kidney, gives rise to the albumin and casts.

The defective circulation to all or parts of various organs affected by vascular disease may be attributed to (*a*) largely irremediable scarrings of the blood vessels and (*b*) more temporarily acting factors which decrease their caliber and elasticity. The degenerated and calcified patches in the blood vessels come under the first of these headings; while under the second may be listed any agency or agencies capable of producing vaso-constriction. For this reason the taking of food (especially protein), muscular work, low degrees of acid intoxication, slight exposure to lowered temperature, etc., all tend to raise the blood pressure of anyone, or to raise further the abnormally high pressure characteristic of the victim of vascular disease. But most important for the arteriosclerotic is the fact that the toxins (amins) of the various infections lead to such vascular spasm. The high blood pressure of vascular disease is therefore compounded of a removable element (due to injurious methods of living and the absorption of poison from infected areas in the body situated in teeth, tonsils, gall bladders, genito-urinary tracts, etc.) and an irremovable element (due to scars of an incurable type in the blood vessels themselves).

It is time that the old argument of whether blood vessel disease leads to high blood pressure or high blood pressure leads to

vascular " degeneration " were settled, and in favor of the former. There is not a particle of physiological, pathological or clinical logic behind the second and all evidence is against it. E. C. VAN LEERSUM'S [1] work on the subject is definitive. In rabbits so operated as to allow of blood pressure readings in perfectly uninjured animals he repeated the observations of NERKING and STEINBISS that the feeding of horse adrenals and liver led to enormous increases in blood pressure (a doubling thereof) for as long periods as such feeding was maintained. But even after weeks of such treatment the animals showed no signs of vascular disease, and their blood pressure fell to normal a few days after their abnormal protein diet was cut off.

The conclusion from such observations is obviously as follows: The blood vessel lesions of vascular disease are the pathological consequences of embolic infection of the vasavasorum; the heightened blood pressure the consequence of the loss in blood vessel caliber and elasticity due to the effects of these embolic infections plus the effects of more temporarily acting poisons derived from the source or sources responsible for the embolic infections, or any other sources capable of originating such materials.

§ 4

The patient before you is at this time better than she was some weeks ago, when we first saw her. What was the scheme of treatment suggested to her, and how did it work? Obviously the fundamental effort in treating patients of this type should be, if our analysis has been made correctly, to relieve the vascular disease. But as you know, the degenerative and scarring changes that occur in vascular disease are not of a reversible kind, and consequently not of a variety that can be "cured." Therefore, our attention can only be directed toward stopping, if possible, the progress of the vascular disease and toward a relief of those signs and symptoms which are the expression of this vascular disease in the different organs.

If it is true that the vascular sclerosis brings about a lack of circulation through the involved tissues, then, obviously, the maintenance of the circulation at its best is a first requisite. It is

[1] E. C. VAN LEERSUM: Pflüger's Arch., **142**, 377, (1911); Zeitschr. f. exp. Path. u. Therap., **11**, 2 (1912); Virchow's Arch., **217**, 452 (1914).

for this reason that resort to so-called blood pressure lowering drugs should not be had too hastily. These may not increase, but may actually decrease, the amount of blood going through a suffering organ. On the other hand, drugs which increase blood pressure, like digitalis or caffein, may actually prove beneficial. This is especially true when the element of cardiac failure, which we shall discuss in the next patient, is bringing about a lowering of blood pressure in these vascular patients.

The lack of circulation produced by vascular disease tends to be expressed in the involved tissues by an accumulation here of carbonic and other acids. The involved tissues will tend, therefore, to become œdematous, which in the case of the brain, for example, is manifested in headache. Obviously acids or similar substances produced by other methods and elsewhere in the body will similarly tend to produce a swelling of the brain. It is therefore of great importance in these vascular patients who may be showing only such apparently mild head symptoms as those of headache, to discover whatever extracranial factors may be at work to produce such substances and to remove them as far as may be possible. It is for this reason that the interdiction of hard muscular or mental labor, of alcohol, a high protein diet, etc., produces such good results. This is simply a method of cutting down the sources of acid production in the body. If we add to it a continuous administration of alkali in amounts sufficient to keep the urine always neutral, we give the different organs involved the best possible chances for getting along on the blood supply still left to them, and so long as we succeed in so doing our patient fares well.

§ 5

But what can we do in our efforts to relieve the vascular disease itself? This evidently depends upon what we hold to be the nature of vascular disease and its cause. Our text-books teach us that hard work, a strenuous life, a high protein diet, lead poisoning and many other things are the causes of this trouble. Thus far no one has proved by experimental means that any of these things really produce an arteriosclerosis, and I think it is a safe gamble that no one ever will. I say this because vascular disease, even in its extremest grades, remains a spotty affection of the blood vessels. In other words, areas of entirely normal blood vessel wall may be

seen in districts where everything else has suffered heavily. It is inconceivable how a soluble poison, like alcohol, for example, could circulate for hours, days, or months, through the blood vessels and destroy only spots in them. Only a spotty cause can be responsible for this spotty destruction. We know at the present time only one method by which such a type of destructive lesion may be produced and that is through a localization of bacteria in these spots, with secondary destruction of the surrounding areas of tissue. And this is, to my mind, what happens in vascular disease. The primary changes in vascular disease occur in the smallest blood vessels of the body. When they involve a large blood vessel, like the aorta, they do so by involving primarily the small blood vessels supplying the large one; in other words, the vasavasorum.

It has long been recognized that the spirochete of syphilis is capable of settling in these small blood vessels and of producing areas of destruction about itself. To it we shall add shortly many other types of organisms which we know now to break into the blood stream periodically and to give rise to embolic infections. Every sufferer from vascular disease must in consequence be looked over carefully for infected tonsils, teeth, antra, ethmoids, hemorrhoids, pelvic organs, prostates, toe nails, etc., which might serve as sources of infection to the general blood stream.

It is because of these views that the patient before you was advised to lose the heavily infected teeth that she carried up to a few weeks ago. In addition she was put upon alkali, a dietary regimen which advised her to eat her vegetables first and then her meat—and I must break in here with the remark that eggs, game and fowl are just as bad (or just as good) as any other protein foods—while a more even life was outlined for her. Her condition has improved considerably. Her headaches have practically gone; she has gained in weight and has not had one angina attack in several weeks. Her systolic blood pressure has fallen to 200 and her diastolic to 110.

§ 6

What is the prognosis in these patients? It depends, evidently, upon the possibility of discovering and of removing the sources of infection which we hold to be responsible for the vascular disease, and then upon the degree to which the vascular disease has pro-

gressed in some one or all of the vital organs. The ordinary patient who is discovered to be a sufferer from so-called chronic interstitial nephritis, but who has shown no head symptoms and no heart symptoms, is one for whom we can make a prognosis that reads "indefinitely good." Causes of death in patients with vascular disease run about as follows: one-third die of such things as may attack you or me—in other words, the automobile accidents of life; of the remainder, one-half die of cardiac failure and the rest of accidents to the cerebral circulation, either hemorrhage or an œdema of the brain, the latter being usually and wrongly diagnosed as "uremia."

As may be obvious to you, therefore, a patient who is not and has not suffered head symptoms when first seen and who has not been dyspneic, or showed a swelling of the feet, or something of the sort, is a fairly good risk. Patients showing such symptoms may be given a good or bad prognosis, depending upon how much of the element in their case is a consequence of irreducible vascular disease and how much is due to such added factors as hard work, intoxication with alcohol, an anesthesia, or some such thing. Where such added elements are missing, as in the very old for instance, who may day after day do nothing more strenuous than sit in their arm chairs, the prognosis is bad; in younger individuals, unconscious perhaps of the state of their blood vessels, even an acute attack of cerebral œdema or something similar does not always portend ultimate disaster if they can be tided over the attack and then be taught to accept a better mode of life. The reasons for this are, of course, clear. In the former type of patients, vascular disease must be regarded as almost exclusively responsible for the head attack; in the second, the vascular condition plays a rôle, but the added and removable elements have played their parts, even more heavily, in the alarming attack which may have been the first to direct attention to the more serious and irremovable elements.

For several years I have not seen one of these patients die primarily of kidney disease. The normal or so-called "increased" urinary output with few casts and little albumin in these cases does, it is true, frequently give way to a decreased urinary output heavily charged with albumin and casts, but, as I shall show you, such change is far more often the consequence of a failing heart than of a vascular disease which has progressed to the point of blotting out the whole of two kidneys.

B. The Cardiac Type with Chronic Interstitial Nephritis.

§ 1

Mr. K., our next patient, is seventy-one years old. He comes to us with a history of having had chronic interstitial nephritis and high blood pressure for ten years past. In spite of this, he has always been well until last spring, when he became somewhat short of breath and noticed a swelling of his feet. His physician put him to bed for two weeks, during which time his shortness of breath and swelling of the feet disappeared, leaving him again able to follow his accustomed routine. About two weeks ago he observed a return of these two symptoms, and as they became steadily worse, he entered the hospital about five days ago. The patient informs us that his blood pressure during the past years has not varied much from 240 mm. of mercury and that analyses of the urine have discovered only traces of albumin.

On examination of the patient we observe that, because of shortness of breath he assumes by preference a half upright position. We have no difficulty in noticing the tortuous and thickened blood vessels on the brow, in the neck, in the arms, at the wrists, in the femoral regions, in the legs and over the backs of the feet. We note also that his pulse beats, as felt at the wrist, are not only irregular in rhythm but uneven in intensity. His radial pulse, as well as we can count it, is one hundred and twenty-two. Both relative and absolute cardiac dullnesses have increased in all directions, as I have indicated by the marks upon his chest. The booming character of the first sound is impaired and none of the heart sounds over the valve areas are pure. There is a marked systolic murmur over the mitral area and a systolic and diastolic murmur over the aortic. The blood pressure as measured to-day is, systolic 161 mm. of mercury, diastolic 88 mm. In examining the patient further we find that the liver dullness extends a hand's breadth below the costal arch in front and that there is some dullness over the lower portions of both lungs posteriorly, the extent of which I have indicated with pencil lines. There is also a ring of dullness low down in the abdomen, evidently due to an accumulation of fluid. The legs are swollen throughout their length, the œdema being most marked in the feet. The nurse informs us that there have been only two voidings of urine in the last twenty-four hours, amounting *in toto* to 420 cc. (fourteen ounces). As I show

you in these tubes, this urine is highly acid to methyl red, and heavily charged with albumin; microscopically we find it filled with granular and hyaline casts.

§ 2

While this type of patient is commonly regarded as presenting the terminal picture of a chronic interstitial nephritis, I think that you will agree with me in holding it more correct to say that he is at this time essentially a heart case. For at least ten years he has been the victim of vascular disease, which, while it seems in this individual to have affected the kidney more than in the previous patient, has never interfered sufficiently with his general well-being to make him conscious of his diseased state. In fact, everything has gone well until last spring when, either because his heart muscle tired of the tremendous labor daily demanded of it, or because the gradually progressing vascular disease involved more extensively his heart muscle, his aortic valves, his aorta, or all of these things together, those obvious signs of impairment in cardiac efficiency which I have detailed to you, entered to dominate the picture.

Note please that everything we see about him is characteristic of heart disease, and nothing justifies our regarding him now as suffering primarily from kidney disease. Note also that his blood pressure is lower than, from his history, it used to be. It is sufficient to emphasize that a falling blood pressure in these patients with vascular disease and so-called chronic interstitial nephritis, when not the consequence of a therapy designed to relieve the vascular condition itself, is always a bad sign, for it means a failing cardiac efficiency.

§ 3

Perhaps some of you would like to insist that this man now has more kidney disease than formerly and that his general condition has grown worse on this account. His kidney state is worse, but for reasons previously discussed not only is this not responsible for his general symptoms and signs—his generalized œdema, for example—but even the extensive kidney involvement now betrayed by his scanty urinary output is not due, in the main, to the vascular disease which originally affected his kidneys. The present

picture is almost totally that of a failing heart. In other words, this patient is in the same state as the man with heart disease whom I showed you earlier in the evening, but the etiology for the heart disease in this patient is somewhat different. To show you how true this is, it is only necessary to inquire as to what therapeutic schemes aid patients of this type most. In spite of the present abnormally high blood pressure, these patients receive most benefit from the administration of digitalis, of caffein, of camphor and of other drugs which *increase* blood pressure by increasing cardiac activity. As a better circulation is obtained, as the products of sub-oxidation are thus better removed and as in this general process more oxygen is brought to the kidney, the urinary output rises, the albumin diminishes, and, if the heart is not too badly affected, these patients may recover completely, as did this patient last spring. Were the kidney changes primary and due to increased involvement of the kidney by the vascular disease, an improvement after cardiac and respiratory stimulation would not be so universal.

§ 4

. We are giving this patient all the alkali he will swallow (he has taken sixty grams of sodium bicarbonate in the last twenty-four hours) but thus far we have not been able to reduce the acidity of his urine to below the turning point of methyl red. We are giving him also several doses of digitalis every day and a dose of magnesium sulphate each morning. We shall feel better about him if we succeed finally in getting his urine neutral and if time gives indication that the aortic and heart muscle lesions are not too severe to prevent a return to a more effective forward movement of the blood. If such improvement does not take place the outlook is grave.[1]

C. The Cerebral Type with Chronic Interstitial Nephritis

§ 1

I need not dwell upon that type of chronic interstitial nephritis in which cerebral hemorrhage closes the picture. In such cases no one ever doubts that the cerebral hemorrhage is secondary to the

[1] The urine of this patient was never made alkaline. The heart rate continued high while the intensity of the individual beats gradually diminished until, about ten days later, many of them failed to reach the wrist. The patient died two weeks after being shown.

vascular disease, so the foolish suggestion is never made that death is dependent upon the kidney involvement. There is, however, another form of cerebral death in which the death *is* held to be secondary to the kidney disease and I think entirely unjustly so. This occurs in those patients for whom has been made a diagnosis of chronic interstitial nephritis with high blood pressure and cardiac hypertrophy and in whom symptoms alleged to be "uremic" close the scene.

Dr. Gallwey has a patient of this type under his care now, but since he has developed a convulsion within the last two hours we do not feel justified in bringing him before you. Suffice it to say that he is a man forty years old, who for a number of years past has shown some casts and albumin in his urine, a systolic blood pressure of 165, a diastolic of 102, a certain amount of cardiac hypertrophy and at no time any œdema anywhere in the body. Three weeks ago he developed drowsy spells, for which he came to the hospital. During the past three days it has been difficult to rouse him, and this evening he has had a convulsion. Every day since he has been in the hospital he has passed about two liters of urine and at no time has this showed more than a trace of albumin and an occasional cast. The chlorid output, the urea output, etc., when due consideration is paid to the character of the food that he is consuming, have always been normal.

§ 2

The patient presents what the clinicians generally diagnose as the "uremia" of chronic interstitial nephritis. After what I have told you, I need not emphasize the erroneousness of such a view. The primary diagnosis here is again vascular disease which has involved different organs in the body. While it has struck the kidney to a certain extent, it has largely spared the heart, but it has affected severely—and we think disastrously—the circulation to the head. What is called uremia in these patients is not secondary to the loss of kidney function, but is an œdema of the brain due to interference with its circulation through the vascular disease. Time after time in my experience, as in this case, I have seen patients lie for days and weeks, and once even for months, in absolute coma, when not one sign pointed to a serious, if in fact any, involvement of the kidney.

What makes the prognosis so bad in these patients is the fact that the œdema of the brain (which in itself is not different from the œdema produced in such a general intoxication as may be incident to pregnancy, or secondary to an anesthetic, starvation, or diabetes) is brought about by a vascular disease so marked that for its relief we can do practically nothing. Even should we succeed in getting this patient out of his coma by the use of alkali, of hypertonic salt, of magnesium sulphate, of dextrose, or by the use of all together, our gain is only too commonly likely to prove temporary for none of these things influence the vascular disease itself which is primarily responsible for the œdema of the brain.

If I have at all succeeded in making myself clear you will by yourselves have come to the conclusion that the mere diagnosis "nephritis" can henceforth mean little or nothing. By itself it only states that certain changes essentially colloid-chemical in character and produced through the action of acids (and certain other substances like urea, pyridin and the amins), have taken or are taking place in the kidney. Having come to such a conclusion, we need to go further and to determine the cause or causes which may be behind the abnormal production and accumulation of these substances in the kidney. In the list may be found anything comprised in the practice of medicine from heart disease through pregnancy and intoxication with heavy metals; the whole category of the acute and chronic, the localized and the general infections; the subtleties of nutritional disturbance and mental anguish. As I have tried to show you, these things express themselves in three main groups of kidney change: first, intoxications originating without or within the kidney and, usually, involving the whole of the organ: second, infections of the kidney involving either pieces, or when sufficiently extensive, the whole of one or both kidneys; third, vascular disease usually affecting limited portions of the kidney, though often progressive in type.

A diagnosis of nephritis must be resolved into its elements; by itself it means no more than a diagnosis reading "headache," "stomach trouble," or "dropsy."

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